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DERMATOLOGIC THERAPY OF YESTERDAY AND TODAY*

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JUST as technology has revolutionized methods of production in industry, so scientific discoveries in medicine have revolutionized methods of medical treatment. This discussion primarily concerns therapeutic changes in the field of dermatology as they have occurred within the past hundred years.

DERMATOLOGIC PROGRESS

Since progress is based on research, the discussion should begin with Ferdinand Hebra, properly known as the father of dermatology. He established a pathologicoanatomic system of skin diseases dividing them into twelve classifications: cutaneous hyperemias; cutaneous anemias; secretion anomalies of cutaneous glands; inflammatory dermatoses; cutaneous hemorrhagies; cutaneous hypertrophies; cutaneous atrophies; benign tumors of the skin; malignant tumors of the skin; cutaneous ulcers; cutaneous neuroses; and parasitic dermatoses. This truly great pioneer in dermatology maintained that no approach to the study of skin diseases could be made other than by the empirical method in view of the lack of any rational basis for dermatologic therapy. Previously, there was a genuine fear that the use of external medication would drive the disease inside. He asserted that since the skin can absorb many forms of bacteria that will enter the circulation, it can also absorb beneficially topical medication. Hence, former fears regarding the use of topical medication were allayed. He introduced diachylon ointment in the treatment of eczema and the water bed in the treatment of pemphigus and extensive burns.

In 1880 an eminent pupil of Hebra, Isidor Neumann, wrote in the preface of his textbook of skin diseases that the etiology of dermatoses was shrouded in darkness, that no solutions had yet been found and that they would perhaps always remain a secret. Obviously, the common therapy at this time included the use of anything and everything, much to the dissatisfaction of Neumann, who insisted that the most effective results would come from the use of external medication. With few exceptions the therapeutic agents employed by both these men are in common use today. A case in point is Neumann's treatment of three common skin disorders: acne vulgaris, psoriasis vulgaris and eczema. In cases of acne vulgaris he removed comedones by an extractor; he used starch-talc powder, green soap, sulfur paste (precipitated sulfur, glycerin, potassium carbonate and alcohol, 25.0 parts of each), glycerin soap, sulfur sand soap, Hebra's spiritus saponis kalinus, 0.1 per cent mercury bichloride solution, Kummerfeld's water (precipitated sulfur, 1.0, camphor spirit, 2.0, lavender spirit, 2.0, glycerin, 5.0, cologne water, 5.0, and purified water, 60.0 parts) and facial steam bath. In acne indurata he used mercurial plaster and scarification and, in acne of the chest and back, Vleminckx's solution (camphor, 6.0, acacia, 6.0, precipitated sulfur, 20.0, and calcium hydroxide solution to make 120.0) and leeches. In cases of psoriasis he did not hesitate to prescribe internal medication such as Fowler's solution and asiatic pills in spite of his emphasis on the use of external medicaments and of his conviction that they were generally the most effective. Water was an important element in the treatment. Cold and warm baths served to macerate the scales. He advocated bathing in mineral springs. He also employed green soap, cod-liver oil, ointments containing ammoniated mercury, chrysarobin, pyrogallol, birch and juniper tars, and tar baths. In cases of acute eczema he used cold soft water in the form of wet dressings, douches and baths, to which were also added astringents such as aluminum acetate, boric acid, cupric sulfate, mercury bichloride and zinc sulfate. In chronic eczema he used ointments containing boric acid, ammoniated mercury, lead oleate plaster, birch and juniper tars.

In 1887 the Boston dermatologist, James C. White, wrote about the influence of diet on skin diseases. He believed that alcoholic beverages and certain acid foods produced or aggravated inflammatory skin affections or acute eczema in some people.

*Dedicated to Professor Emil Meirowsky, eminent dermatologist and pioneer in pigment research, on his eightieth birthday.
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Henry G. Piffard, one of the founders of American dermatology, wrote in 1891 of the importance of etiology. He made the significant statement that internal causes are far more frequent and important than those of external origin. He continued with the traditional use of external and internal medicaments.

Earlier in his career Moriz Kaposi, the closest associate of Hebra, had already stated that the true understanding of dermatoses is founded on important ideas of basic medical science, particularly general pathology and histopathology. Later, he again stressed the fact that it is important to make a correct diagnosis and to know the effects of the individual application of each medication to obtain successful results. He followed the same therapeutic procedures that had previously been used although he did not see any reason to forbid salty and spicy foods, fish and alcoholic beverages. Finally, from practical experience, he found that the best treatment for acute eczema with intense swelling and copious weeping was the use of wet dressings of diluted Burow's solution.

Paul Gerson Unna brought physics, chemistry, bacteriology and histology into the study of dermatology. He based his rational diagnosis and therapy on microscopical analysis of dermatoses. Neither Hebra nor any of his pupils had recognized any organic connection between etiology, histology, clinic and therapy. On the basis of macrochemical and microchemical experiments Unna discovered new therapeutic methods and became the founder of modern scientific dermatologic therapy. He introduced salve mulls and plaster mulls. One of these plaster mulls, composed of 40 per cent salicylic acid (salicylic acid plaster, 40 per cent) is still successfully used in the treatment of plantar warts. Medical practice is indebted to him for the invention of serviceable adhesive tape. He brought into common use a new ointment base, anhydrous eucerin (aquaphor), which serves as a principal element in an excellent cooling ointment.

Oscar Lassar and Unna independently and simultaneously produced a zinc paste (Lassar's consisting of zinc oxide paste with salicylic acid *N.F.*, and Unna's of purified siliceous earth, 5.0, zinc oxide, 25.0, oil of benzoin, 10.0, and benzoinated lard, 60.0 parts). Unna also made a cooling paste (prepared chalk, 25.0, zinc oxide, 25.0, linseed oil, 20.0, wool fat, 6.0, and calcium hydroxide solution, 24.0 parts).

Additional medications that Unna created were salve pencils, resin pencils for the removal of hair, particularly in ringworm of the scalp in children, the superfatted soap (basis soap), also with additional medicaments, ichthammol (ichthyol), anthralin (Cignolin) and a zinc-glycerin-gelatin mixture (zinc gelatin, *U.S.P.*) for the treatment of varicose ulcers and pruritic dermatoses. He also introduced a comedo extractor and a microcautery in the treatment of pustular skin lesions and small growths.

I cannot enumerate the many distinguished dermatologists who practiced on the basis of the findings of the Austrian, German, English and French schools; however, with the discovery of x-rays and radium and the introduction of the carbon-arc and mercury lamps the therapy of cutaneous diseases was revolutionized. Nils Finsen was the first to treat tuberculosis of the skin with his carbon-arc lamp. Of special interest to dermatologists was the introduction of the water-cooled mercury-vapor quartz lamp by Ernst Kromayer.

In 1905 Pusey innovated the use of solid carbon dioxide for the treatment of warts, superficial vascular nevi and small benign tumors. He suggested its use as a substitute for liquid air, formerly utilized by James C. White and others.

That same year Kromayer described the use of dental burs and rasps as well as punches for the removal of small benign tumors, warts, nevi, freckles, acne lesions and small scars. He employed very fine drills for the removal of comedones. Most of his early operations were performed without anesthesia. For sensitive patients he recommended Schleich's local anesthesia, and for larger areas of the face, ethyl chloride. In removing freckles he used a carbon dioxide stick to induce anesthesia. Kromayer's methods were not without flaws and therefore were not generally accepted.

Owing to the efforts of Max Joseph and his collaborators, cosmetology became a part of scientific dermatology.

A boon to civilization was Paul Ehrlich's discovery of salvarsan for the treatment of syphilis. With this chemotherapeutic approach, acridine dyes like acriflavine and Rivanol were used for the treatment of infectious dermatoses. These drugs were later superseded by newer, more effective ones.

In the early twenties, J. F. Schamberg expressed a sentiment that applies equally today — namely, that modern publications do not keep abreast of the rapid modification of medical judgment concerning the various new types of treatment.

William Allen Pusey, an outstanding American dermatologist, stated what all must recognize and admit: although there are innumerable therapeutic agents available, actually only a few are capable of combating the pathologic conditions that confront physicians in their patients, and the empirical approach must still operate.

I think it is safe to sum up the achievements of the past by saying that the generally accepted procedure consisted of more external than internal treatment, an empirical approach to the problem as a whole and a reliance upon more or less successfully used external medicaments, together with radiation therapy when called for. Dermatologists today are continuing with even greater emphasis on wider research. Until the cause or causes of skin disorders have been discovered one must necessarily try with caution every reasonable remedy advanced by those in the field.

During the past twenty years momentous develop-

ments in dermatologic therapy have taken place and have produced a twofold effect. On the one hand, certain new medications influence the pathologic process as such, and on the other, they carry the danger of sensitizing the skin organ to a degree rarely experienced before. This period has seen the advent of sulfonamides, antibiotics and antihistamines. Many of these drugs cannot be applied topically because of their high sensitizing index. Of all the new products that have come into being during the last decade, the corticosteroids must be mentioned particularly for their dramatic results in the treatment of pemphigus and systemic lupus erythematosus.

Contemporary Dermatologic Therapy

Up to this point I have dealt at some length with the basic contributions of the past and have acknowledged dermatology's debt to them; now I should like to take up the broad outline of today's therapy based upon my own personal experience and observations of over thirty years. It is axiomatic that a correct diagnosis produces effective therapy. When there is an underlying organic disease, subsequent treatment hinges upon its proper recognition and management. Like all dermatologists, I apply both external and internal treatment as the case may require.

There is no question that internal medication would be the ideal treatment for cutaneous diseases, particularly of organic origin. It is regrettable that at the present time knowledge of etiology is still limited. Often, internal therapy is empiric or symptomatic. A good illustration is the way in which corticosteroids function. So long as they are administered, the skin condition usually improves or subsides, but when they are discontinued, very often the original skin disorder recurs, sometimes in even worse form than before corticosteroid treatment. The fact that various dermatoses respond readily to the administration of corticosteroids permits the supposition that intrinsic factors such as hormones and enzymes could be responsible for the origin of some dermatoses. Sommers and I concluded from histochemical experiments that a mucinase might conceivably be implicated in the etiology of psoriasis.

For internal medication, various antibiotics are useful in widespread, superficial or deep-seated infections of the skin. Streptomycin is available in the treatment of tuberculosis of the skin. Since nystatin (Mycostatin) is a very recent drug, no objective conclusions can be drawn regarding its effectiveness in the treatment of generalized moniliasis. Specific serum therapy is indicated in diphtheria of the skin. Autohemotherapy is at times helpful in the management of urticaria. No specific method has yet been found for the prevention of plant dermatitis. The internal use — either by mouth or by injection — of various Rhus extracts is of no benefit. On the contrary, while the acute dermatitis exists, administering such extracts aggravates it.

What place have vitamins in dermatology? I believe that their use is limited. Vitamin A may be effective in a few patients with follicular hyperkeratosis suffering from severe deficiency of that vitamin; vitamin B complex, particularly nicotinamide, is necessary in pellagrous dermatitis; vitamin D_2 is used in the treatment of tuberculosis of the skin. I have found vitamins to be ineffective in the treatment of acne, psoriasis, seborrheic dermatitis and chronic discoid lupus erythematosus.

Antihistamines are at times beneficial in urticaria. Chloroquine phosphate and quinacrine hydrochloride are at the present time the most satisfactory drugs in the treatment of chronic discoid lupus erythematosus. Chlorpromazine hydrochloride and rauwolfia compounds are of certain value as tranquilizing drugs in eczematous conditions and in psoriasis when psychogenic factors are involved. These two drugs have no direct effect on pruritus or the disease itself. Isoniazid is presently the most satisfactory drug in the treatment of skin tuberculosis because of its harmlessness and thoroughly quick action. Combined with sulfones it is used in the treatment of leprosy. Androgenic and estrogenic hormones give equivocal or questionable results in acne. I rarely prescribe them. Corticosteroids have utmost effectiveness in pemphigus and in systemic lupus erythematosus. Their use in acute, generalized dermatitis (contact and medicamentosa types), atopic dermatitis, exfoliative dermatitis, severe erythema multiforme and erythema nodosum, and urticaria must be critically evaluated in each case.

Some other drugs may be prescribed internally or given as injections in various skin conditions: salicylates as an antipruritic and analgesic; codeine sulfate as an analgesic; barbiturates, chloral hydrate, paraldehyde and others as sedatives; sulfonamides in widespread infections of the skin, and sulfapyridine particularly in dermatitis herpetiformis; psoralen derivatives in vitiligo; arsenic in dermatitis herpetiformis and lichen planus (this last medication must be strictly supervised by the physician); diluted hydrochloric acid in rosacea; yellow mercurous iodide in flat juvenile warts; gold sodium thiosulfate in chronic discoid lupus erythematosus; and potassium iodide in deep-seated mycoses such as blastomycosis and sporotrichosis. Recently, stilbamidine has been recommended for some deep-seated mycoses. In some skin disorders a special diet is recommended; however, the results are not consistent in all cases — for example, in acne vulgaris, eczema, psoriasis vulgaris, rosacea, urticaria and xanthoma. Occupational hazards, the widespread use of cosmetics and related substances and various synthetic products, as well as certain medications given both internally and externally, often cause dermatoses whose treatment is dependent entirely upon removal of the cause.

As new agents are developed one should demand that they not be released for general use before they

have been tried out on a large scale by at least several critical investigators who are experienced clinicians. In this connection paired symmetrical comparisons may be useful. Physicians must have exact knowledge of the pharmaceutical properties of the agents to be used, and they must be familiar with their proper application.

In his therapeutic endeavor the physician should differentiate the treatment for acute, subacute and chronic dermatoses. He must remember that a chronic skin condition may suddenly show signs of acute inflammation that demands a quick therapeutic change. He should never prescribe ointments in acute dermatitis. "Nil nocere" (do not do harm) must be the guiding principle in the therapy of all dermatoses. Topically used agents with a high sensitizing index ought always to be avoided. In such a category belong penicillin and some other antibiotics, sulfonamides, antihistamines, nitrofurazone (Furacin) and local anesthetics.

An acute dermatitis should be treated with powders, principally talc, open wet dressings, baths, shake lotions or drying, greaseless pastes, according to the stage of the inflammation. Cold or at times warm aqueous solutions of aluminum acetate or boric acid (1:50 parts of water) may be applied. Weak aqueous solutions of lead subacetate, sodium borate, potassium permanganate and silver nitrate may also be used. I do not intend to challenge the opinion of physicians who believe that wet applications of water alone have the same effect as those with ingredients added to the water. The outcome of careful comparative experiments will decide this issue in the future.

If vesicles, pustules and bullae are present in acute dermatitis or acute dermatophytosis they must be drained.

A shake lotion (zinc oxide, 25.0, talc, 25.0, glycerin, 20.0, and purified water, 50.0 parts) or a drying, greaseless paste with bentonite (zinc oxide, 25.0, talc, 25.0, glycerin, 20.0, and bentonite magma, 50.0 parts) is preferred by me in the treatment of acute and subacute dermatitis without oozing. If the skin becomes too dry after the use of the two prescriptions mentioned above, Lassar's zinc oil (zinc oxide and olive oil, 60.0 parts of each), Unna's soft zinc paste (prepared chalk, 25.0, zinc oxide, 25.0, linseed oil, 20.0, wool fat, 6.0, and calcium hydroxide solution, 24.0 parts), zinc paste *(U.S.P.)* and Unna's hard zinc paste (purified siliceous earth, 5.0, zinc oxide, 25.0, oil of benzoin, 10.0, and benzoinated lard, 60.0 parts) may be used.

In generalized eruptions with intense pruritus lukewarm or warm starch or oatmeal baths are useful.

Soaps and soap substitutes should be avoided in acute and subacute dermatitis. Synthetic detergents are widely used as soap substitutes. It is my opinion that their usefulness is overrated. Lukewarm water, alcohol, petroleum benzin, olive and linseed oils function well as cleansing agents.

In chronic dermatoses it may be necessary to use each variety of application and agent before successful results are obtained. Soft pastes and ointments constitute the most important therapeutic agents in chronic dermatoses. A skin sensitive to ointment bases is best treated with shake lotions, drying, greaseless pastes or zinc oil.

Petrolatum, yellow or white, is the cheapest hydrocarbon ointment base. It is a well tolerated emollient and permits the incorporation of various medicaments, but not of water or aqueous solutions. If water-miscibility is desired, hydrophilic petrolatum *(U.S.P.)* may be used. Other useful emollients are animal fats such as lard and wool fat and vegetable oils such as almond, linseed, olive, persic and theobroma oils.

As a cosmetically acceptable absorption base I prefer aquaphor, a cholesterolized petrolatum, which permits the incorporation of water or aqueous solutions up to 350 per cent. Another absorption base of the water-in-oil type is hydrous wool fat.

Hydrophilic ointment *(U.S.P.)* is relatively greaseless and is the example of a water-removable or water-washable base. It is an oil-in-water emulsion, and may be removed from the skin or hair by washing with water.

A water-soluble, greaseless base is polyethyl glycol ointment (*U.S.P.*). I rarely use it since it is not well tolerated by the skin. Excellent bases of both water-in-oil and oil-in-water types are commercially available. To obtain the desired therapeutic effects, the physician must know the physical characteristics of the ointment bases to be used.

Numerous medicaments may be added to the various ointment bases. Antieczematous agents are salicylic acid (up to 3 per cent for keratoplastic effect and 3 to 40 per cent for keratolytic effect); resorcinol, particularly in concentrations of 10 per cent and more for keratolytic effect; precipitated sulfur, 0.5 to 10 per cent; mercuric sulfide, 0.25 to 0.5 per cent; ichthyol, 1 to 10 per cent; bismuth subgallate, 1 to 2 per cent; various tars, such as crude coal tar, juniper tar, pine tar and Wright's liquor carbonis detergens, 0.25 to 10 per cent; lead oleate plaster, 10 to 50 per cent; and pyrogallol, 2 to 5 per cent. Antipsoriatics include salicylic acid, 2 to 5 per cent; 2 per cent in combination with ammoniated mercury, 5 to 10 per cent; and anthralin, 0.1 to 1 per cent (not to be used on the face). Antipruritics comprise salicylic acid, 0.25 to 2 per cent; menthol, 0.125 to 1 per cent; and carbolic acid, 0.25 to 1 per cent.

Some of these medicaments may be prescribed in combination, although incompatible mixtures are to be avoided. Lotions and ointments containing hydrocortisone acetate (1 per cent), fluorohydrocortisone acetate (0.1 per cent) and prednisolone (0.5 per cent) are widely used in eczematous conditions of the skin. It is my opinion that these preparations have their best effects when applied to itchy, eczematous

conditions of the skin of the eyelids, ear canals and genitoanal regions. Their cost makes their use prohibitive over a long period or over an extensive area. Care must be exercised because of potential systemic effects.

Other forms of topical therapy include the following: 5 to 10 per cent pine tar in alcohol, 70 per cent for lichenified eczema; 20 per cent podophyllum resin in alcohol, 90 per cent or 25 per cent podophyllum resin in compound benzoin tincture for condylomata acuminata; 5 to 10 per cent formaldehyde solution in diluted alcohol for hyperhidrosis of the hands and feet; 10 per cent salicylic acid collodion as a keratolytic agent for the treatment of corns and warts; zinc gelatin (*U.S.P.*) as a paint for chronic eczema and as a bandage (Unna's boot for varicose ulcer); and 40 per cent salicylic acid plaster for calluses, corns and plantar warts — an excellent remedy if used over a long period in conjunction with paring the surface of the keratotic lesion. Caustics include liquefied phenol, trichloracetic acid and silver nitrate in 5 to 10 per cent aqueous solution or as a pencil.

A great many topical preparations containing antibiotics are available for the treatment of pyogenic infections of the skin. Lotions and ointments may be used. Because of a low sensitization index bacitracin, neomycin sulfate, polymyxin B sulfate and tyrothricin are recommended. The Council on Pharmacy and Chemistry of the American Medical Association recently recognized the discriminate use of dermatologic preparations of chloramphenicol, chlortetracycline and other broad-spectrum antibiotics. It is my contention that one should not expose a patient to the risk of sensitization to a topically applied antibiotic that he may later need for the treatment of a serious internal infection. In spite of antibiotic therapy it is necessary to drain pustular lesions of all sizes mechanically.

As antifungal agents fatty acid preparations are widely used. It is my opinion that fatty acids applied in powder form have a certain value in fungous infections of the feet although they are not superior to 10 to 50 per cent boric acid powder. Fatty acid preparations incorporated in an ointment very often sensitize the skin. In chronic fungous infections of the skin 2 per cent salicylic acid combined with 2 to 5 per cent precipitated sulfur incorporated in an ointment or Sabouraud's tincture of iodine in alcohol, 70 per cent (1:5), have proved their value over the years. I also believe that the newer antifungal agents have no superior effect in fungous infection of the scalp in children in comparison with precipitated sulfur and Sabouraud's tincture of iodine. No real fungicidal agent for fungous infection of the skin, nail and hair has yet been found. Nystatin (Mycostatin) may prove to be of value, particularly when incorporated in a lotion, for localized cutaneous moniliasis.

As an antiparasitic agent 10 per cent DDT powder is effective for the eradication of pediculi. I prefer an ointment containing 10 to 25 per cent precipitated sulfur in the treatment of scabies. Newer antiscabietic preparations are also effective. Benzyl benzoate often causes irritation of the skin.

I consider an ointment containing 2 per cent salicylic acid and 2 to 10 per cent precipitated sulfur the best antiseborrheic preparation. Selsun suspension (selenium disulfide, 2.5 per cent) is useful as a shampoo in the treatment of seborrhea of the scalp. It should be applied with caution.

Dermatologic therapy also includes physical methods. Refrigeration in the form of solid carbon dioxide or dry ice is useful in the treatment of superficial angiomas and warts. There are only a few indications for actinotherapy in dermatology. Ultraviolet-light therapy shortens the course of pityriasis rosea when given in erythema dose. It is also used beneficially when combined with tar medication in the treatment of some cases of psoriasis. Ultraviolet-light therapy in other chronic recurrent dermatoses is of questionable value. The use of the air-cooled mercury vapor lamp, known as the Kromayer lamp, applied with pressure stimulates the regrowth of hair in alopecia areata.

X-ray and radium therapy is another useful modality in dermatology. Its administration requires special training. Acute dermatoses should not be treated with x-rays or radium. X-ray therapy is a valuable form of treatment in *Microsporum audouini* infections of the scalp in children and in malignant tumors of the skin. It should be used discriminately in chronic dermatoses. Acne, psoriasis, superficial fungous infections of the glabrous skin and many cases of chronic eczema are not benefited by x-ray therapy. Radium is used particularly in the treatment of malignant tumors of the skin and in hemangiomas of children. X-ray and radium therapy may be beneficial in some cases of keloids of recent origin. High-energy electron therapy has recently been recommended in the treatment of generalized superficial dermatoses, lymphoblastoma and Kaposi's sarcoma. Radioactive isotopes are also utilized in dermatologic therapy. Grenz-ray therapy is not superior to x-ray therapy. The treatment of port-wine stains with Grenz rays is ineffective. Thorium-X, incorporated in an ointment, alcohol or lacquer may be useful in some localized chronic eczematous conditions, especially of the scalp and scrotum, where x-ray therapy is contraindicated.

Indications for cautery, electrocoagulation and electrodesiccation are manifold: pustular and cystic lesions in acne; rosacea; warts; small benign skin growths, including some pigmented nevi; hemangiomas; and some epitheliomas of the skin. Epilation by long-wave or short-wave diathermy is used in localized hypertrichosis. I may also mention here the beneficial use of injections of sclerosing agents in hemangiomas.

Frequently, a dermatologic condition requires a surgical approach. Surgery may range from the removal of comedones by the comedo extractor to the excision of a malignant tumor of the skin. Between these two extremes there are many other indications for surgery of varying degree: manual epilation of hair in folliculitis, sycosis simplex and ringworm of the scalp in children by epilating forceps; drainage of abscesses and furuncles by scalpel; opening of vesicles and pustules in dyshidrotic conditions by scissors; removal of warts, mollusca contagiosa and seborrheic keratoses by dermal curette; and biopsy and removal of benign and malignant tumors of the skin by scalpel, diathermy wire loop or punch.

More recently, surgical planing or dermabrasion of acne scars has become significant. In 1949 Schreus described the use of carborundum grinding wheels for the mechanical removal of superficial and deeper skin lesions such as nevi, tattoos and warts. Kurtin should be credited with having introduced his method of surgical planing of acne scars with a motor-driven wire brush. He used ethyl chloride as a local anesthetic. The introduction of dichlorotetrafluoroethane, a noncombustible, nontoxic refrigerant anesthetic, has simplified the method. Dermabrasion represents at the present time the best treatment for the improvement of acne scars after the active acne has subsided. Satisfactory results can also be achieved by dermabrasion in the treatment of aged skin of the face showing wrinkles, keratoses and pigmentations. It must be emphasized that critical selection of suitable cases is of utmost importance so that the dermabrasion will not fall into disrepute because of poor results.

Discussion

Finally, it should be pointed out that proper care of the skin is essential and that in some skin conditions an environmental change may be beneficial. Emotional factors can play a part in the development and course of some skin disorders. Although these factors must be adequately dealt with, the psychosomatic aspect should not be overrated, and the appropriate dermatologic treatment should not be neglected.

In this paper I have traced the development of dermatologic therapy over the past hundred years. Although considerable progress has been made there is still a very long row to hoe before results can be designated as entirely satisfactory. It is to be hoped that continuous research will bring greater knowledge of the etiology of cutaneous diseases and that, as a result, specific remedies will be found to cure the most plaguing skin disorders. Only then can dermatologists truly advance their branch of medicine and uphold its distinguished tradition.

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EXTRADURAL SPINAL-CORD HEMATOMA*

Report of a Case Due to Dicumarol and Review of the Literature

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DICUMAROL (3,3'-methylenebis-4-hydroxycoumarin) is a well established agent in the prevention and treatment of embolism and intravascular thrombosis by virtue of its ability to depress prothrombin formation. It was early found that the clinical use of this anticoagulant might be accompanied by hemorrhage, which has been reported as commonly occurring in the genitourinary tract, brain and cerebral meninges, postoperative wounds, pleural cavity, skin and gastrointestinal tract. Other sites of hemorrhage include the retroperitoneal tissues (sometimes after lumbar sympathetic block), the pericardial cavity and joints. The case presented below is unusual in that an extradural spinal-cord hematoma developed secondary to Dicumarol therapy. Only 2 previous cases of this kind have been reported. Prompt and proper treatment of this syndrome can prevent paraplegia and possible death.

CASE REPORT

A 57-year-old engineer was first admitted to the hospital on June 21, 1950, complaining of pain in the left arm and left side of the chest. There was a previous history of gout and arteriosclerotic and hypertensive cardiovascular disease. Electrocardiographic studies indicated posterior myocardial infarction, and he was given Dicumarol. Daily prothrombin-time determinations were performed for 28 days, and after discharge, the patient was kept on a routine of 50 mg. of Dicumarol daily for 5 days, followed by a 2-day interval without medication. The interval between prothrombin-time determinations was gradually increased over a period of several months until he was maintained on the schedule mentioned above, with determinations each week at the end of the 5-day period of medication. During a 6-month period, the lowest prothrombin time was 9 per cent, and the highest 30 per cent. The last recorded preadmission prothrombin time, on January 10, 1951, was 14 per cent (36 seconds, with a control of 14 seconds). Symptoms began 4 days later, with pain in a wide area across the lower back when the patient rose from a chair. No trauma or straining preceded the onset. Findings at that time were straightening of the lumbar spine, pain bilaterally at the level of the 3d lumbar segment when he performed spinal movements and an anteflexed position on standing or walking. Neurologic examination was negative, with bilaterally equal and somewhat hyperactive knee and ankle jerks. There was no immediate progression of the symptoms, which, in fact, gradually improved over a period of several days on therapy with aspirin, codeine and rest on bed boards. On January 18 backache became worse, and severe pain was noted in the backs of the calves and thighs. Because this pain resembled that of previous attacks of gout, the patient treated himself with colchicine, which on previous occasions had relieved his gouty symptoms. This medication failed to relieve him. The knee and ankle jerks were still equal and active that evening, and the prothrombin time was 15 per cent (31.2 seconds, with a control of 12.5 seconds). On the next morning he felt better but still noted backache and aching in the backs of his legs. At this time several brownish-blue discolorations were observed on the thigh. Repeated questioning revealed that the left 5th toe had been numb for about 2 days, with pins-and-needles sensations in the soles of his feet since the previous evening. He was admitted to the hospital on January 19.

Physical examination on admission showed a short, stocky man lying in bed crossing his legs alternately, ankle above knee, every few minutes. The blood pressure was 200/110. The eye grounds showed vascular sclerosis, without hemorrhages or exudates. There was a purplish macular area, 1 by 2 mm., in the buccal mucosa. The heart was percussed 2 cm. to the left of the mid-clavicular line. There was a normal sinus rhythm, without murmurs. He was unable to stand because of lower-extremity weakness. There was mild bilateral weakness of dorsiflexion of the feet, with intact plantar flexion. Quadriceps function was impaired bilaterally although he was capable of straight-leg raising. The knee jerks were depressed, more on the left. The ankle jerks were absent. The plantar responses were normal. Sensory examination showed no saddle anesthesia. The only sensory impairment was numbness of the left 5th toe and hypesthesia to light touch of both soles. The skin revealed several areas of brownish-blue discoloration on the forearms and thighs. There was normal anal-sphincter tonus. The initial impression was arteriosclerotic and hypertensive cardiovascular disease, history of old posterior myocardial infarction, history of gout and Dicumarol toxicity manifested by bleeding in the lower spinal cord.

Microscopical examination of the urinary sediment showed 8 to 10 red cells per high-power field. The prothrombin time was 7 per cent (54.2 seconds, with a control of 12.5 seconds). The white-cell count was 4500, with 77 per cent neutrophils.

Within an hour of admission the patient was given 500 ml. of blood and 75 mg. of vitamin K (Synkayvite) intravenously. During the evening of the day of admission, a marked increase in the leg and back pain occurred, and an additional 500 ml. of whole blood and 100 mg. of Synkayvite were administered. Paresthesias were noted in the lower legs and feet. The prothrombin time on the next morning was 42 per cent or 17 seconds (control, 12.5 seconds). However, there was progressive weakness of the lower limbs, and areflexia developed. Overflow micturition occurred, and an indwelling catheter was inserted. Sensory loss had progressed to include the posterior aspect of the left thigh, the plantar surfaces of both feet and the dorsal and plantar surfaces of all toes. Anal-sphincter atonia and gluteal paralysis developed. A spinal tap, previously deferred for fear of aggravating bleeding, was performed in the 4th to 5th lumbar interspace.

Clear-yellow cerebrospinal fluid under normal pressure (160 mm. of water) was obtained. After 5 ml. was removed the final pressure dropped to 50 mm. of water. Emergency myelography was performed by the use of 1 ml. of Pantopaque. The area below the 3d lumbar segment was visualized as normal. Opposite the 3d lumbar segment the column stopped abruptly, and even in the 60° head-down position for 4 minutes, it failed to proceed upward. The shape of the Pantopaque defect suggested an extradural block, the lowermost border being at the 3d lumbar segment (Fig. 1 and 2). Shortly before operation there was noted to be almost complete loss of motor function of the legs, only weak quadriceps function remaining.

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On January 20 laminectomy (1st, 2d and 3d lumbar vertebras) was performed. At this level a dark-red, partially organized clot with superimposed fresh clot was found overlying and compressing the spinal cord extradurally. After removal of the clot the dura was opened, and yellow fluid exuded, followed by a gush of clear fluid under pressure. A small catheter was gently passed upward and downward within the dural sac, substantiating the fact that the block had been relieved. To control persistent venous oozing, Gelfoam was liberally applied, and several Penrose drains were left in place for 24 hours.

FIGURE 1. *Lateral View (Pantopaque in the Dural Sac), with the Patient in Head-down Position.*
Anteriorly, the Pantopaque column is flat. Posteriorly, there is a curved depression because of the extradural clot.

The postoperative course was characterized by a gradual return of motor power and sensation. Urologic examination, including a cystometrogram, revealed an automatic "cord" bladder with very good sensation. A bilateral vasectomy was performed prophylactically. On April 3 transurethral resection was performed, after which the patient had complete urinary control and voided adequately with suprapubic pressure. On examination 1 year postoperatively he could walk about 100 feet on crutches, stand unaided for short periods and take half a dozen unsupported, though shaky, steps. He could dress and bathe himself and carry on his daily activities without help, and he was having a daily bowel movement. There was normal anal-sphincter tonus and sensation. Sensory return was complete except for hypesthesia of the soles and hyperesthesia over the dorsa of the feet. Major remaining motor weaknesses were in both gluteal groups and in the dorsiflexors of the feet.

DISCUSSION

The anticoagulant drugs represent a two-edged sword by virtue of rendering the blood relatively incoagulable. The necessity for frequent and reliable prothrombin-time determinations has been stressed. This is particularly important in patients on long-term anticoagulant therapy. The use of weekly prothrombin-time determinations is a common outpatient procedure once the patient's tolerance to Dicumarol has been adequately observed.[1] In the case presented above, a weekly determination was performed. Although no change in dosage was made, symptoms of an extradural spinal-cord hemorrhage began four days after a prothrombin time of 36 seconds (14 per cent) was determined. The occurrence of back pain in a patient receiving Dicumarol should have aroused suspicion at that time. The patient's schedule consisted of 50 mg. of Dicumarol daily for five days followed by two days without medication. The possibility must be raised that colchicine or aspirin, alone or acting in synergy, aggravated the bleeding in this case.[2] Certainly, initiation of bleeding was unassociated with any drug other than Dicumarol since aspirin was not given until back pain appeared and colchicine was not ingested until definite neurologic signs became manifest.

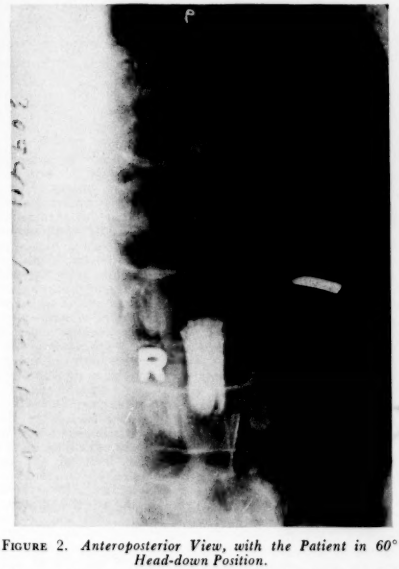

FIGURE 2. *Anteroposterior View, with the Patient in 60° Head-down Position.*
The Pantopaque column is blocked at the level of the third lumbar segment.

The presence of 8 to 10 red cells in the urinary sediment, noted on January 19, 1951, was a warning of excessive anticoagulant effect. One of the earliest papers on Dicumarol reported the frequent occurrence of microscopic hematuria.[3] Routine urinalysis appears to be a valuable adjunct in the early diagnosis of Dicumarol toxicity. The use of vitamin K_1

oxide has been reported to be more effective than vitamin K in a number of experimental and clinical studies.[4,5] If an extradural hemorrhage of the spinal cord is suspected the early use of myelography will substantiate the diagnosis, after which operation should be performed forthwith. To defer spinal tap because of the fear of aggravating quiescent bleeding may result in an unnecessary delay in surgical therapy.

Extradural hematoma of the spinal cord is a rare clinical entity. It may occur in vertebral fractures as part of the disruption of tissues in the area of fracture.[6] It has been reported in stillborn infants as one of multiple traumatic effects.[7] It may occur rarely in blood dyscrasias such as leukemia[8] and hemophilia,[9,10] as well as with toxic febrile illnesses.[8] However, only a few adequately documented cases of isolated extradural spinal-cord hematoma have been found in the literature.

Jackson,[11] in 1869, described a fourteen-year-old girl with spontaneous onset of weakness in the fingers followed by progressive weakness of the upper extremities and muscles of respiration. Post-mortem examination revealed a large extradural clot of the entire cervical cord.

In 1897 Bain[12] described an extradural hematoma in a young woman at the level of the second and third cervical segments found at post-mortem examination. The patient had strained heavily at stool on the day of onset of quadriplegia and had taken some unknown type of pills on the preceding evening.

Hopkins,[13] in 1899, reported the case of a man who had back pain while shoveling snow, followed by paraplegia and death. Autopsy showed a lumbar extradural hemorrhage.

Jonas[14] (1911) described a farmer who fell from a hayloft, with immediate loss of motor power, followed by sensory loss over a twenty-four-hour period. Ten days after the accident an extradural clot was removed at the level of the sixth and seventh thoracic segments, with recovery of leg function.

In 1925 Reid and Kennedy[15] presented the case of a young woman who was pushed from her bicycle by a passing auto. On the following day, leg and back pain occurred. Paralysis occurred three days later, followed by death. Autopsy revealed a hematoma from the third cervical segment to the lumbar region.

Hassin and Stone[16] described a young woman with subacute combined degeneration of the spinal cord who fell with resulting urinary retention, leg paralysis and spinal block two days later. A hematoma at the tenth dorsal segment was removed, with subsequent improvement, but the patient succumbed to her primary disease two weeks postoperatively.

Verbrugghen,[17] in 1946, reported the case of a patient in whom a cervical extradural hematoma developed after a fall. Removal of the clot was followed by excellent recovery.

Chavany et al.[18] reported the case of a seventy-year-old woman who noted the spontaneous onset of severe lumbar backache progressing to sensory and motor paraplegia. Lipiodol injection and manometrics revealed an incomplete block. A large organizing hematoma was found from the level of the first lumbar to the upper border of the fourth lumbar vertebra. The postoperative recovery was good.

Shenkin, Horn and Grant,[19] in 1945, described 3 cases of extradural spinal-cord hematoma, 1 of which, however, was associated with a toxic febrile illness; a second was associated with a spinal-column fracture. In the third case, a forty-two-year-old man noted weakness in both legs after a sudden turn in bed. This progressed in two hours to complete lower-limb paralysis. Laminectomy a week later revealed an encapsulated hematoma from the second to the fifth thoracic segment, with a pale underlying spinal cord. There was still no return of function five months later.

Four years later Kaplan and Denker[20] reviewed the literature and added 2 cases of their own. One was in a thirty-nine-year-old woman who vomited during an attack of cholecystitis. This was followed by severe back pain and rapid onset of paraplegia. Four days after the onset of the paraplegia, laminectomy revealed an extradural hematoma at the fifth and sixth thoracic segments. A twenty-week follow-up study showed no return of lower-limb function. A second case was that of a forty-three-year-old man with sudden progressive paralysis of both lower limbs while shaving. Laminectomy twelve days after onset demonstrated an extradural hemorrhagic mass whose upper border was at the ninth thoracic segment. Though temporary sensory return occurred, this regressed, and paraplegia was the result on follow-up study.

Svien et al.[21] described a sixty-seven-year-old man who fell on his buttocks, without immediate disability. Two weeks later he noted bilateral leg pain and backache. On admission, ten months after the fall, a lumbar extradural hematoma was removed, with complete recovery. The case simulated a ruptured disk, and the authors pointed out that spinal-cord hematoma is another possibility in the many differential diagnoses of low-back pain and sciatica.

In 1952 Devanney and Osher,[22] at the Clinical Pathological Conference of the Cincinnati General Hospital, discussed a case similar to that presented above. The patient was a sixty-two-year-old man receiving Dicumarol for acute thrombophlebitis. The onset of low-back pain was followed by pain radiating down the posterior aspect of both legs, and later by urinary retention and numbness and weakness of the legs. Myelography revealed a posterior block. Surgery was delayed because of a low prothrombin time. Laminectomy was performed on the seventh day after the onset of symptoms, and an extradural clot overlying the second to the fifth lumbar segment

was removed. Eventual recovery was apparently almost complete.

Arieff and Pyzik,[23] in 1954, reported a case of paraplegia associated with excessive Dicumarol therapy. This may have been due to epidural bleeding, but exploration was not performed and the authors considered hematomyelia the likeliest cause of the paraplegia.

In the following year Cloward and Yuhl[24] described a sixty-six-year-old man who had both extradural hematoma and subdural bleeding while receiving Dicumarol therapy. Partial recovery followed evacuation of the blood.

Though the cases in the literature are commonly divided into spontaneous and traumatic varieties, the probable cause in many of the so-called spontaneous cases has been varying amounts of mild trauma or straining. The case reported above, as well as those of Devanney and Osher and Cloward and Yuhl, probably must be placed in a separate category since they are neither strictly spontaneous nor traumatic.

Verbrugghen[17] states, "Following indirect trauma to the spine, the short progressive history with the gradual onset of paraplegia in a few minutes or a few hours and the absence of a bony lesion should strongly suggest extradural hemorrhage of the spinal cord." The present case report suggests that if such a patient is receiving anticoagulants the possibility of localized bleeding must be considered even more likely, even though there is no history of trauma.

Summary and Conclusions

A case of spinal-cord extradural hematoma in a patient receiving Dicumarol is presented. This syndrome masqueraded as lumbosacral strain until neurologic signs and subcutaneous ecchymoses appeared.

Fourteen well documented cases of extradural hematoma of the spinal cord previously reported in the literature are reviewed. This is the third recorded case ascribed to Dicumarol toxicity. This diagnosis should be entertained in any patient receiving anticoagulants in whom low-back or sciatic pain develops.

The use of spinal tap and simplified Pantopaque myelography established the diagnosis. Surgery, although only partially successful, was followed by considerable improvement. Earlier intervention might have yielded better results.

The need for frequent prothrombin-time determinations is emphasized. Repeated examinations of the urinary sediment for red cells in patients receiving Dicumarol seem indicated.

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EXACERBATION OF PRE-EXISTING NEUROLOGIC DISEASE AFTER SPINAL ANESTHESIA*

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THE chief dissatisfaction with spinal anesthesia centers about the neurologic complications that are probably indigenous to the method. In an attempt to clarify this problem we undertook a long-term study of this technic.[1] The results were encouraging. In 89 per cent of 10,098 spinal anesthetics followed for six months to five years, there was no case of severe progressive neurologic disease. The major share of the lesser sequelae were related to lumbar puncture[2] and are largely preventable by a careful technic. Certain minor neurologic defects were noted; none were progressive, and none of any consequence.[3] These, too, it is believed, can be kept to a minimum by attention to asepsis and choice of reliable local anesthetics.

Another and important means of prevention of neurologic disease after spinal anesthesia involves the proper selection of patients. Afflictions of the central nervous system and spinal column are contraindications. This has been a basic tenet in anesthesia but never a thoroughly documented one. In our reported series of cases, despite care in selection, spinal anesthesia was given inadvertently to 11 patients with pre-existing neurologic disease. One other case of interest has been added. The results of this trespass provide the subject matter of the present report.

MATERIAL AND CASE REPORTS

The method of discovery of these cases is worthy of comment. During a four-year period, from 1948 to 1951, patients receiving spinal anesthesia at the Hospital of the University of Pennsylvania were interviewed preoperatively for suitability regarding choice of anesthesia. During anesthesia the details of lumbar puncture and of the anesthetic given and the results obtained were recorded in every case. After anesthesia the patients were seen consistently and questioned for specific complications. Six months later a questionnaire was sent to all, and the returns were screened for replies indicating onset of neurologic disease. Subsequently, many personal interviews and physical examinations were done. Out of the welter of complaints, no doubt heightened by the method of study, the cases of disease reported below were discovered (Table 1).

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This is the fourth of a series of papers based upon a study and long-term follow-up results of 10,098 spinal anesthetics.

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Spinal-Cord Tumor

A previously present but symptomless spinal-cord meningioma produced symptoms in the immediate postoperative period. Lack of alertness early and, later, preoccupation with the idea of a relation to spinal anesthesia delayed diagnosis and curative treatment.

CASE 1. A 42-year-old housewife with pain in the left side of the abdomen and chest was operated on for the repair of a diaphragmatic hernia. Lumbar puncture was performed with a 22-gauge needle at the 4th-5th interspace. A transient paresthesia was produced in the left leg, but the cerebrospinal fluid was clear and dripped freely. Spinal anesthesia to the level of the 5th thoracic dermatome was obtained with Pontocaine and glucose. Postoperatively, the patient complained of backache. Before she left the hospital a note was made of heaviness in the legs and tingling sensations in the toes. Six months later the reply to the routine questionnaire stated that she had gradually become incapacitated with backache, falling episodes, spreading numbness, loss of strength and paresthesias in the legs.

On examination the following neurologic defects were found: ataxia, a Romberg sign, a Babinski sign on the left, absent abdominal reflexes, diminished to absent position sense in the legs, hypesthesia to pinprick to the level of the 10th thoracic dermatome, partial loss of motor power in the left leg and spasm of the back muscles. Blood counts were normal, blood serologic tests were negative, and free hydrochloric acid was present in the gastric juice. Normal cerebrospinal fluid, pressure and dynamics were found on lumbar puncture. The protein content of the cerebrospinal fluid was 47 mg. per 100 ml.; the Kolmer test was negative. Cells were not present. A cystometrogram disclosed a hypotonic bladder. X-ray examination of the back showed degenerative and hypertrophic changes in the thoracic spine. Myelography was avoided because of the suspicion that arachnoiditis was present. Physical therapy was the prescribed treatment.

A year after the spinal anesthesia a typical meningioma was found at laminectomy in another hospital. Postoperatively, there was rapid improvement. Six months later the patient had recovered completely.

This complication was the most serious in the entire series. For several months it was interpreted as a case of adhesive arachnoiditis. Kennedy et al.[4] have written that neurologic disease consequent to spinal anesthesia occurs after a latent period unbeknown to surgeon and anesthetist. This might have taken place in the case reported above if there had not been a special study in progress. There was no latent period, but early symptoms were not heeded. Later, although other diagnoses were entertained, adhesive arachnoiditis seemed the most likely to all concerned. Myelography would have established the correct diagnosis. Whether the introduction of a radiopaque material into the subarachnoid space would have been additionally harmful in the presence of arachnoiditis is a debatable point.[5] There is a characteristic roentgenographic picture for arachnoiditis.[6] Early surgical exploration appears to be indicated in a problem of this nature.

The unusual features for a diagnosis of either arachnoiditis or tumor were the normal cerebrospinal-fluid dynamics and normal protein level. A block should be demonstrated to establish the diagnosis of either disease although Poppen and Hurxthal[7] have advanced reasons why dynamics may be normal in tumor suspects. The early onset of symptoms of spinal-cord compression by tumor after lumbar puncture can be attributed to displacement of the mass or to vascular engorgement. An alteration in cerebrospinal-fluid pressure rather than the injection of the spinal anesthetic is responsible for these changes. Michelsen[8] and Nicholson and Eversole[9] have had a similar experience with spinal-cord tumors and spinal anesthesia. Michelsen suggests that the dynamics of the cerebrospinal fluid and the protein content be tested routinely in spinal anesthesia. We believe, with Nicholson, that this is impractical. A spinal anesthetic should not be injected, however, if lumbar puncture yields a suspicious-looking fluid or if flow or aspiration of fluid is not free.

Viral Disease of the Central Nervous System

Two cases are discussed under this heading. The first represents the possible relation between an acute infection, herpes zoster, spinal anesthesia and the subsequent appearance of neurologic disease.

CASE 2. A 25-year-old woman with right-lower-quadrant abdominal pain was operated on for acute appendicitis. Spinal anesthesia to the 6th thoracic dermatome was obtained with Pontocaine and glucose injected through a 22-gauge needle inserted at the 3d-4th lumbar intervertebral space. One tap was made without production of paresthesia, and the cerebrospinal fluid was clear. At operation the appendix was not markedly inflamed. On the 2d day after operation herpetic lesions appeared on the left side in the distribution of the 6th and 7th thoracic dermatomes. These lesions remained for 4 weeks and were treated with ergotamine. Three weeks after operation pins-and-needles sensations arose in both thighs, with radiation down the backs of the legs. At the same time there was severe backache, with difficulty in straightening the trunk. The sensory disturbances lasted for 12 days, and the backache for 2 weeks. A month after anesthesia diminished appreciation of pinprick was elicited over the outer surface of the right foot and anterior surface of the tibia. A week or so later these signs had disappeared, leaving the patient with a cooler right foot. The only complaint after a year was a subjective difference in temperature in the legs.

TABLE 1. *Antecedent Neurologic Disease and Postoperative Neurologic Sequelae.*

CASE NO.	NEUROLOGIC DISEASE	AGE	SEX	OPERATION	LUMBAR PUNCTURE	ANESTHETIC	POSTOPERATIVE SEQUELAE
		yr.					
1	Undiagnosed spinal-cord meningioma	42	F	Diaphragmatic herniorrhaphy	Paresthesia of left leg; cerebrospinal fluid clear.	Pontocaine; glucose.	Progressive sensory & muscular changes; cure by laminectomy.
2	Undiagnosed herpes zoster	25	F	Appendicectomy	Atraumatic; cerebrospinal fluid clear.	Pontocaine; glucose.	Transient sensory & muscular defects of leg
3	History of mumps encephalitis	36	F	Cholecystectomy	Atraumatic; cerebrospinal fluid clear.	Pontocaine; glucose; epinephrine.	Headache; recurrence of weakness of leg; recovery.
4	History of cerebrovascular accident; leg pain; hemiparesis; bladder weakness.	59	F	Diagnostic spinal anesthesia	Multiple spinal taps	0.2% procaine	Exacerbation of leg pain & bladder weakness
5	History of sciatic pain	59	M	Suprapubic prostatectomy	Atraumatic; cerebrospinal fluid clear.	Pontocaine; glucose.	Reappearance of leg pain; recovery.
6	History of sciatic pain	53	M	Appendicectomy; excision of Meckel's diverticulum.	Atraumatic; cerebrospinal fluid clear.	Pontocaine; glucose.	Reappearance of pain; laminectomy; disk removed.
7	History of backache	68	F	Resection of renal cyst	Paresthesia on left; cerebrospinal fluid clear.	Pontocaine; glucose; epinephrine.	Reappearance of backache
8	Spinal-column tumor metastases	77	M	Abdominoperineal resection of colon	Atraumatic; catheter spinal.	Pontocaine; glucose.	Back & leg pain after 6 mo.
9	Metastatic melanosarcoma	50	M	Abdominal exploration	Atraumatic; cerebrospinal fluid clear.	Pontocaine; glucose; epinephrine.	Delayed onset of back & leg pain; urinary incontinence.
10	Diabetes; anemia; arteriosclerosis.	68	M	Suprapubic prostatectomy	3 taps; cerebrospinal fluid clear.	Pontocaine; glucose.	Leg weakness; sensory changes.
11	?Diabetic neuropathy	75	M	Suprapubic prostatectomy	Atraumatic; cerebrospinal fluid clear.	Pontocaine; glucose.	?Foot drop; absent vibratory sense.
12	Acute otitis media	12	M	Diagnostic spinal anesthesia	Atraumatic; cerebrospinal fluid clear.	Procaine (5%)	Meningismus or meningitis 12 days postoperatively

An attractive hypothesis is that spinal anesthesia was administered in the presence of an acute nervous-system infection, that of herpes zoster. The resulting neurologic signs represented, then, a combination of damaging influences. Herpes zoster is an infectious disease caused by a filtrable virus with a predilection for the posterior-root ganglion, posterior nerve roots and horns.[10] Persistent sensory and motor paralysis can result. A similar neurologic defect can follow spinal anesthesia. Thus, one cannot establish in this case a clear relation between neurologic defects on

the one hand and spinal anesthesia and herpes zoster on the other.

Another possibility is precipitation of trophic lesions of a herpetiform type by spinal anesthesia. This was one of the explanations offered by Carter[11] for a herpetiform eruption arising after lumbar puncture. Trauma may be the cause if the lumbar-puncture needle injures a ganglion. It is known that herpetiform eruptions can be produced in the distribution of a nerve root by manipulation of the root.[10] Arnold[12] found herpetic eruptions in 3 cases after 640 spinal anesthetics; there was no relation to the lumbar-puncture site, and he assumed that a toxic nerve injury had occurred. Despite these hypotheses, it seems wise to eschew spinal anesthesia if a diagnosis of viral disease can be made before operation. This admonition is borne out by the report of Nicholson and Eversole[9] of a case of varicella and spinal anesthesia followed by neurologic deficit.

The question is often asked if it is safe to give spinal anesthesia to a person who has recovered from a central-nervous-system viral infection. Poliomyelitis is usually the disease involved, but the following report of mumps encephalitis is an instructive one.

CASE 3. A 36-year-old woman who was 152 cm. (5 feet) tall and weighed 88.5 kg. (195 pounds) was scheduled for a cholecystectomy. She was in the 3d month of pregnancy and gave a history of eclampsia, hypertension and jaundice. Lumbar puncture was performed without paresthesia with the use of a 22-gauge needle inserted at the 3d-4th lumbar vertebral interspace. The cerebrospinal fluid was clear and flowed freely. Spinal anesthesia to the 5th thoracic dermatome was achieved with Pontocaine, glucose and epinephrine. Immediately after operation the patient experienced weakness of the right leg and diffuse impairment of sensation to pinprick. A mild transient postural headache lasted for 2 days. Within several days the leg seemed stronger, but, on the 10th postoperative day, it buckled under her when she attempted to stand. At this time she volunteered the information that she had had mumps followed by convulsions and encephalitis 10 years previously. Both her legs had been affected at that time, especially the right, which weakened on exertion. When she was seen as part of the spinal-anesthesia follow-up study 3 years later the right leg, though much stronger, continued to annoy her with intermittent pain.

Spinal anesthesia seemed to precipitate symptoms that had been dormant for years. A history of encephalitis was not elicited in the preoperative visit despite specific inquiry for antecedent neurologic disease. For one reason or another many patients forget important events in their lives during history taking. One can only speculate on the reasons for recrudescence of disease. It may be significant that the maximum concentration of anesthetic in the subarachnoid space came in contact with the lumbar nerve roots on the previously affected right side. We have reason to believe that the local anesthetic injected may be responsible for the appearance of sensory changes.[3] Since the vascularity of the spinal cord is important in the development of some peripheral neurologic syndromes[13,14] perhaps vasoconstriction brought about by epinephrine added an ischemic insult to an already damaged area. One must not neglect the role of the psyche in this case or of a decrease in cerebrospinal-fluid pressure suggested by the postural headache; the latter could aggravate a cerebrovascular process responsible for the peripheral symptoms in the first place. Reference is made below to a reappearance of neurologic symptoms when spinal anesthesia was given to a patient with an old cerebrovascular accident.

Degenerative Disease of the Central Nervous System

In this category we include cerebrovascular disease and its complications, combined sclerosis, disseminated sclerosis, syphilis and amyotrophic lateral sclerosis. One is frequently confronted with selecting an anesthetic for a patient with one of these diseases. In reference to problems of this kind Yaskin and Alpers[15] wrote, "It is a well recognized fact that the first clinical manifestation of some clearly defined nervous disorder may date from a severe trauma, operation or confinement." Critchley[16] adds, "spinal anesthesia also may be a precipitating agent in the evolution of such affections as disseminated sclerosis, progressive muscular atrophy or syphilis." The following case falls into this general category.

CASE 4. A 59-year-old woman had had a cerebrovascular accident followed by a left-sided hemiparesis and urinary-bladder weakness 6 years before entry. These complaints had cleared considerably, but she was left with intractable leg pain, mostly on the right. As a diagnostic and prognostic measure for pain, a differential spinal anesthetic by a continuous technic was given with 0.2 per cent procaine. Multiple taps were made with a 16-gauge needle. A paresthesia was produced in the right foot, but the cerebrospinal fluid was clear. A No. 3 ureteral catheter was inserted 3 cm. into the subarachnoid space. Although a sensory level of anesthesia to the 4th thoracic dermatome was obtained, the pain was not relieved. After anesthesia the pain in the legs increased. A typical postural headache, bladder "weakness" and frequency followed. All eventually cleared.

Bladder "weakness" might have represented retention and overflow incontinence since the patient was receiving large quantities of morphine for alleviation of pain. Exacerbation of leg pain could have been due to an irritative effect of the spinal anesthetic. From time to time after spinal anesthesia, we have seen persons with leg cramps that we were at first willing to ascribe to irritation. However, similar complaints were found in a control series given general anesthesia.[3] Postural headache occurs in a high percentage of persons given continuous spinal anesthesia because of the large needle used for lumbar puncture. In this case the role of decreased cerebrospinal-fluid pressure that the headache represents cannot be determined in reference to the development of neurologic signs.

Backache and Sciatic Pain

Backache is a common complaint after both spinal and general anesthesia. When followed by sciatic pain, backache becomes a potential neurologic prob-

lem since there may be protrusion of an intervertebral disk and compression of a spinal nerve root. The 3 cases we reported below had a common pattern: that of recurrence of backache and sciatica after spinal anesthesia. The symptoms and signs strongly suggested disk protrusion. Although questioned before anesthesia, none of the 3 patients admitted to having had back pain.

CASE 5. A 59-year-old man was given spinal anesthesia with Pontocaine and glucose for a suprapubic prostatectomy. Lumbar puncture was performed with 2 insertions of a 22-gauge needle. Pain and paresthesias were absent. The cerebrospinal fluid was clear. On standing 2 days postoperatively, he experienced severe low-back pain, with radiation to the left foot, both aggravated by straining. At this time he told of having had shooting pains in the left leg before anesthesia. A week after anesthesia, examination disclosed right-sacroiliac tenderness and straight-leg raising limited to 70°. Roentgenograms of the back showed increased density of bone, extensive osseous degenerative disease in the lower lumbar and sacral regions, marginal lipping of the vertebras and narrowing of the 4th-5th lumbar intervertebral space. He improved with Buck's extension traction to the affected leg. On follow-up study 10 months later recovery was complete.

CASE 6. A 53-year-old man, after an attack of abdominal pain, received a Pontocaine glucose spinal anesthetic for an appendectomy and excision of a Meckel diverticulum. Two lumbar taps were made with a 22-gauge needle. The cerebrospinal fluid was clear but did not aspirate well. Six months later he reappeared with left-sided sciatic pain, which had begun 2 months after operation. He also volunteered the information that he had had recurrent low-back pain for 5 years before anesthesia. The recent leg pain was accentuated by coughing and straining, which produced paresthesias to the left calf. Examination disclosed a rigid back, with spastic muscles, tenderness in the left sacroiliac notch, limited straight-leg raising, an absent ankle jerk and diminished sensation to pinprick over the 5th lumbar dermatome. A diagnostic lumbar puncture and insertion of Pantopaque outlined a large herniated disk at the 4th-5th lumbar interspace. At laminectomy the disk was removed. Several months later the patient had obtained considerable relief but wore a back brace and still had positive neurologic signs.

CASE 7. A 68-year-old woman received a Pontocaine glucose epinephrine spinal anesthetic for excision of a cyst of the right kidney. One lumbar puncture was performed, with the production of a paresthesia to the left ankle. Clear cerebrospinal fluid was obtained. Immediately after operation she complained of backache. She admitted then to having had backache for years. Later in the postoperative period, leg pain was thought to be due to phlebitis. Heparin was given. Six months later backache became quite severe. All measures to relieve the complaint had failed. More recently the use of bed boards and paravertebral nerve blocks also had failed. The diagnosis of protruded intervertebral disk was entertained.

There are many reasons why backache, if present before anesthesia, should preclude the use of the spinal technic. Although backache is just as common after general anesthesia, specific reasons can be offered for its occurrence after spinal anesthesia. Traumatic lumbar puncture, though not a factor in the cases reported above, may injure a disk or the structures of the spine.[17] Hemorrhages beneath the ligaments can act as foci of pain, with radiation to a dermatome and with sciatic reference. The psychologic aspects can by no means be neglected since it is natural to relate pain and tenderness at the lumbar-puncture site to co-existing backache. This was a frequent statement in the replies to our follow-up queries. Some believe that muscular relaxation and positioning on a flat operating table cause back strain. Other positions on the table — the lithotomy, for example — surely can produce strain for which the anesthetic is blamed.

The situation is even more complex when a protruded disk is already present. In some clinics[18] spinal anesthesia is selected for laminectomy and operations on the back. Persisting pain and neurologic deficit after operations for protruded disk are sufficiently frequent that we do not recommend spinal anesthesia for this type of procedure. If diagnostic myelography has been performed, development of arachnoiditis from that source is not unheard of.[8] Whenever a foreign substance is injected into the subarachnoid space, such a possibility exists. Finally, arachnoiditis has been found at a second laminectomy for persistent backache.[19,20] This was thought to be due, in some cases, to the trauma of the first operation.

Metastatic Cancer of the Spine

Unsuspected tumor metastases to the spine may be present when spinal anesthesia is given. Nicholson and Eversole[9] reported a case of spinal-cord compression after anesthesia due to metastatic tumor. The following cases are illustrative of problems encountered in this sphere:

CASE 8. A 77-year-old man was given a Pontocaine glucose continuous spinal anesthetic for an abdominoperineal resection of the rectum. Lumbar puncture was performed with a 16-gauge needle after 2 insertions without pain or paresthesia. The cerebrospinal fluid was clear. A sensory anesthetic level to the 4th thoracic dermatome was obtained. Six months later shooting pains in the left hip and anterior aspect of the thigh, with radiation to the knee, developed. A question of arachnoiditis was raised by the consulting neurologist, but roentgenograms of the back showed destruction of the 1st 3 lumbar vertebras by metastatic tumor.

CASE 9. A 50-year-old man had an enucleation of the left eye in 1942 for melanosarcoma. Nine years later he was given a Pontocaine, glucose and epinephrine spinal anesthetic for an emergency abdominal operation. Lumbar puncture was atraumatic, and the cerebrospinal fluid clear. At laparotomy multiple tumor metastases had seeded the peritoneum, and a large metastatic mass was resected with the omentum. Postoperatively, x-ray examination of the chest showed pulmonary metastases. Six months later he wrote that, on leaving the hospital, he could hardly walk because of low-back, coccygeal and leg pain. He had since been receiving medicine by the clock for relief of pain. Urinary incontinence followed by obstinate constipation appeared 5 months after operation. His comment about spinal anesthesia was instructive: "I would not choose this anesthetic for myself or recommend it to anybody else. My nervous system was unstrung. Due to the condition of the nerves it has settled in my bladder." His neurologic examination was not remarkable except for patchy numbness to pinprick in the left sacral region.

Aside from the possibility that lumbar puncture has heightened the symptoms, the most important aspect of the relation between anesthesia and spinal-column disease is the likelihood that the patient will associate possible cause and effect. He is usually encouraged in this belief by his physician, since the

prospect of death from metastatic disease is a hard matter to discuss with a patient. Usually, the possibility of complications from spinal anesthesia dominates the thoughts of consultants, and more likely causes for disease are relegated to a secondary role. In Case 8 arachnoiditis was the diagnosis offered until x-ray examinations were performed. Mistaken diagnoses have been made again and again, sometimes to the detriment of the patient. One must be objective and not blame spinal anesthesia until other conditions have been ruled out.

Diabetes, Senescence and Peripheral Neuropathy

Operations on diabetic patients are often performed under spinal anesthesia since it is a method that adds little to the existing metabolic imbalance. But the diabetic patient is often one with complicating disease. Old age, vascular disease and peripheral neuropathy are accompanied by neurologic signs and symptoms that may be confused with complications of spinal anesthesia. The following reports are of interest in this regard.

Case 10. A 68-year-old man with severe diabetes, prostatic obstruction and hematuria underwent a prostatectomy. Spinal anesthesia with Pontocaine and glucose was administered through a 22-gauge needle inserted at the 3d-4th lumbar interspace. Three insertions of the needle were made; the cerebrospinal fluid was clear, and a sensory level to the 10th thoracic dermatome was obtained. Postoperative bleeding and a transfusion reaction left him with anemia. The hemoglobin fell from 78 to 51 per cent (Sahli). The postoperative course was marked by tachycardia, fever, mental confusion, phlebitis and wound sepsis. Two months later he complained of weakness and lack of control of his legs dating from his hospital stay. Although there had been subjective improvement, examination disclosed a questionable Romberg sign, hyperactive reflexes and a semishuffling gait. A month later weakness of the muscles of the left leg and a stocking type of hypesthesia were discovered. Thereafter, his symptoms abated considerably. One year after operation he was working as a barber, standing most of the day, but with a sense of weakness in the legs.

A few details are lacking that could make this picture more interpretable. The extent of control of the diabetes, the adequacy of circulation to the legs, and the blood and spinal-fluid serologic tests are not known. At any rate, the symptoms and signs could have resulted from spinal anesthesia alone. These improved, however, and we are inclined to attribute them to a multiplicity of things: anemia, vascular disease, poor diabetic control and nutrition and possibly peripheral neuropathy.

Case 11. A 75-year-old diabetic patient had a suprapubic prostatectomy performed under spinal anesthesia with Pontocaine and glucose. An atraumatic lumbar puncture produced clear cerebrospinal fluid. Soon after the operation he felt a "slapping" tendency in the right foot as he walked. There was questionable impairment of dorsiflexion. Vibratory sensation at the knees and ankles was absent bilaterally. However, reflexes were present, pathologic reflexes were absent, other senses were normal, and there was no atrophy. Three months later, when he was interviewed and examined, his intellect was quite clear. He had coarse tremors of the hands, but abnormal neurologic signs were lacking. The slapping tendency of the foot was still present. After 3 years without further progression of the disease he suddenly fell dead.

The common denominator in these cases seems to be a combination of diabetes and old age. It does not seem necessary to implicate spinal anesthesia since either of these conditions can produce neurologic signs in itself. The same complications have been seen after general anesthesia. However, one cannot eliminate the possible additive effect of the trauma of lumbar puncture or of the local anesthetic injected into the subarachnoid space. Peripheral neuropathy associated with diabetes is not uncommon, especially in severe or uncontrolled disease and in the aged.[21] An increased protein content of the cerebrospinal fluid in diabetes has been found when peripheral neuritis was present.[22] So far as advancing age is concerned, a progressive decrease in vibratory sensibility is seen.[23] There are changes in the nerve roots with age[24] and in the spinal cord.[25] This, then, is the soil on which spinal anesthesia is given to the aged diabetic patient. The statement of Thorsén[26] that medullary lesions after spinal anesthesia are more frequent over the age of fifty is a significant one.

Meningitis

Meningitis has ceased to be a problem in spinal anesthesia with increased understanding of the need for an aseptic technic. We discovered no case of meningitis arising in direct association with anesthesia, but report a case of meningitis arising after twelve days. The discovery of coincident acute purulent otitis media makes for interesting speculation.

Case 12. A 12-year-old mentally retarded boy with incapacitating bilateral pes planus was given a diagnostic procaine spinal anesthetic to rule out an element of spasm in his orthopedic problem; anesthesia to the level of the 12th thoracic dermatome was obtained through a 22-gauge needle inserted at the 3d-4th lumbar interspace. One lumbar puncture was performed, with the recovery of clear cerebrospinal fluid. A mild headache was present for 2 days afterward. Twelve days after anesthesia there was an abrupt onset of frontal headache, neck stiffness and a temperature of 102.4°F. The blood pressure was 110/70, the pulse rate 100, and the respirations 24. Purulent secretion was seen in the right auditory canal. The ear drum was injected. Marked stiffness of the anterior and posterior cervical muscle groups was elicited, with reference of pain to the forehead and low back. Brudzinski and Kernig signs were present.

The white-cell count was 8100. Lumbar puncture produced grossly clear cerebrospinal fluid with 20 red blood cells and 150 white cells per cubic millimeter, of which 60 per cent were neutrophils and 40 per cent lymphocytes. The protein content was 58 mg., and the sugar 56 mg. per 100 ml., and the chloride 118 milliequiv. per liter. The initial pressure was equivalent to 220 mm. of water. A culture was negative. Within 24 hours of the start of treatment with crysticillin and chlortetracycline signs and symptoms completely disappeared. The child was completely well at the time of the 6 months' follow-up examination.

The interval between anesthesia and the onset of meningitis tends to eliminate anesthesia as the cause of meningitis. Meningismus and meningitis are not uncommon in association with acute otitis media. The early disappearance of symptoms and paucity of cerebrospinal-fluid changes suggest the diagnosis of meningismus rather than bacterial meningitis. Despite these contentions there is good reason to believe that spinal anesthesia should not be administered in

the presence of infection, especially if blood-stream invasion is a possibility. Weed et al.[27] were able repeatedly to produce experimental meningitis in several animal species by performing occipital or lumbar puncture within five hours of injecting pathogenic bacteria intravenously. Meningitis began not at the spinal puncture site but intracranially, and the injected bacteria were recovered from the subarachnoid space. Thus, the concept has been established of a lowered area of resistance to infection created by spinal puncture. Others[28] have reported the development of meningitis in human patients when spinal anesthesia was associated with acute infectious disease. We believe, therefore, in the exercise of caution when considering spinal anesthesia for operations complicated by infection. An opposing influence is the desire to employ some form of regional anesthesia when the toxicity of infection might be enhanced by general anesthetics.

Discussion

The case histories of 11 patients who showed exacerbation of neurologic disease after spinal anesthesia have been discussed. This group of complications was discovered during a long-term study and follow-up examination of 10,098 spinal anesthetics. The purpose of the study was to clarify the nature and incidence of neurologic sequelae. The patients with antecedent neurologic diseases found were as follows: a patient with a spinal-cord tumor; a patient with herpetiform lesions; a patient with healed encephalitis; a patient with a degenerative disease that may have resulted from a cerebrovascular accident; 3 patients with protruded intervertebral disks; 2 patients with metastatic cancer of the spine; and 2 patients with diabetes and possible peripheral neuropathy. We believe that the undesirable results of spinal anesthesia in these cases emphasize the necessity for careful selection of patients for this method of anesthesia. If this practice of selection is followed and, as previous studies have shown, spinal anesthesia is given with a considered and meticulous technic, neurologic sequelae will be transient and minor in severity.[1-3]

Additional conclusions may be drawn from this experience. In a few cases spinal anesthesia was given to persons with known pre-existing neurologic disease. This should not have been done. In several cases major neurologic disease was brought to light for the first time after anesthesia. These were unavoidable circumstances. We were chagrined to find in most of the remaining cases that, in spite of preanesthetic interviews, a history of antecedent disease was not elicited. The facts were discovered only after complications arose. This can only mean that the anesthetist must take a detailed neurologic history of his own, even at the expense of suggesting to the patient the possible development of disease.

It should not be assumed that a cause-and-effect relation between anesthesia and recrudescence of neurologic disease was established in every case in this series. On the contrary, a new process ascribable to anesthesia could not be established in any. Of the cases with fatal termination, there seemed to be an inexorable progression of the disease that had begun long before the anesthetic was given. In others spinal anesthesia introduced previously symptomless disease, which was cured after the correct diagnosis was made. Regarding diagnosis, we have learned to be objective. Preoccupation with the idea of spinal anesthesia as the inevitable cause of complications in Case 1 led to an erroneous diagnosis (and a costly one for the patient). Consultants who are biased and unfamiliar with modern technics of anesthesia are apt to ascribe any sequela to the anesthetic. Hence, the anesthetist must be sufficiently acquainted with neurologic signs and symptoms to establish the proper diagnosis.

Failure to implicate spinal anesthesia explicitly by no means lessens the caution to be exercised in the choice of anesthesia. There are other reasons why spinal anesthesia should not be given when contraindications have been found. Every patient is willing to blame the anesthetic when he cannot rationalize his troubles otherwise. For some this rationalization is a helpful substitute for a realistic approach to the problem of prolonged illness and approaching death. It is not fair to the reputation of spinal anesthesia to court invidious comparisons by the careless application of this technic.

Conclusions

The conclusions seem quite clear. They have been stated before. Although a cause-and-effect relation between spinal anesthesia and exacerbation of disease has not been shown, spinal anesthesia should not be given to a patient with affliction of the central nervous system or spinal column. This admonition applies to congenital, healed, inactive and active disease. It embraces trauma, bacterial and viral infections, degenerative diseases, neoplasms and systemic diseases with neurologic accompaniments. Exceptions to the rule may be made only when a type of anesthesia other than spinal is potentially more hazardous or less safe in the hands of the person administering it.

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ACUTE ENCEPHALITIS WITH INTRANUCLEAR CELLULAR INCLUSIONS*

A Nonfatal Case of Probable Herpetic Etiology Diagnosed by Biopsy

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IN 1933 Dawson[1] reported the finding of intranuclear inclusions within nerve and glial cells of the central nervous system in a fatal case of encephalitis in man. Since then, no less than 33 additional fatal cases have been recorded in the literature.[2-19] Although most authors agree that the pathological findings suggest a viral etiology, this was established in only 4 of these cases. In each the patient had an acute illness, and the virus of herpes simplex was recovered from the brain at autopsy.[12-15] The illness in most of the remaining cases was subacute or chronic, and the pattern of clinical and of pathological findings similar. In lieu of an etiologic diagnosis, these have usually been classified as "inclusion encephalitis" (subacute inclusion encephalitis), a term introduced by Dawson in his original paper. At least 3 examples of this condition are to be found in papers on subacute sclerosing leukoencephalitis by Martin et al.[10] and van Bogaert.[19]

Foley and Williams[11] and Van Buren[9] recently reviewed the subject of "inclusion encephalitis," and Haymaker[15] has presented a comprehensive analysis of the clinical and pathological features of the proved cases of herpes-simplex encephalitis. It is the purpose of this report to present the first case in which the diagnosis of encephalitis with intranuclear inclusions was established during life by biopsy of the brain. An additional point of interest is that the patient has survived for over two and a half years and partially recovered, thus providing documentation for the previously expressed notion that this type of illness is not invariably fatal.[8,11] Serial serologic studies, though not conclusive, suggest that encephalitis in the present case was caused by the virus of herpes simplex.

CASE REPORT

A 20-year-old soldier came to the Emergency Room of the United States Army Hospital, Fort Campbell, Kentucky, on June 22, 1953. He complained of headache, anorexia, nausea and vomiting for 1 day. The temperature was 101.8°F., but otherwise the examination was recorded as negative. He was stated to be "stoical" and to "minimize complaints." Early heat exhaustion was suspected, and he was admitted to the hospital and treated with 1 liter of isotonic saline solution intravenously. During the night he became confused and restless and talked irrationally; he stated that the fluid given intravenously was "poison." Later that night the temperature was 102°F., the pulse 96, and the respirations 20. He hiccuped continually and, because of marked excitement, disorientation and obstreperous behavior, was transferred to the closed psychiatric ward. During the morning of June 23, the temperature rose to 104°F., and the pulse to 110. The peripheral white-cell count was 11,650, with 65 per cent neutrophils and 35 per cent lymphocytes. Urinalysis was negative. During that day he became increasingly stuporous, and a stiff neck developed. A lumbar puncture was done; the cerebrospinal fluid was clear and colorless, and contained 488 cells per cubic millimeter, of which 33 per cent were polymorphonuclear leukocytes and 67 per cent lymphocytes. On the next day the patient was transferred to the contagious-disease ward, where another lumbar puncture was performed. The initial pressure was equivalent to 350 millimeters of water. The fluid was clear and colorless but contained 457 cells per cubic millimeter, with 48 per cent polymorphonuclear leukocytes and 52 per cent lymphocytes. The total protein was 144 mg., and the sugar content 69 mg. per 100 ml., at a time when the blood sugar was 81.5 mg. per 100 ml. The spinal fluid was sterile.

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The patient was treated with intramuscular injection of penicillin, streptomycin and adrenocortical extract. The blood pressure remained stable at about 150/75. On the same day (3 days after onset of the illness) he became less responsive and incontinent. The temperature remained about 104°F. by rectum. Respirations became labored and irregular. He was examined by one of us (C.W.C.) 48 hours after admission, when he was stuporous though partially arousable and could, on request, grasp with the right hand but not with the left hand. The pupils measured 4 mm. in diameter, were equal and constricted in response to light. The eyes moved conjugately. The fundi appeared normal. Occasional choreoathetoid movements of the left upper extremity were noted. The knee jerk was more active on the left, and the left plantar reflex was extensor. No other reflex abnormalities were noted. Roentgenograms of the skull showed a calcified pineal gland that was displaced to the left.

Ventriculography was done on the 5th day of the disease. Intraventricular pressure was high, and the brain herniated through the dural opening. On the ventriculogram, the septum pellucidum was 14 mm. to the left of the mid-line, and the posterior portion of the right temporal horn of the ventricle was elevated. Ventriculography was followed by a craniotomy and exploration of the right temporal lobe. The brain was swollen, hemorrhagic and soft. The brain herniated through the wound, and much of this area was amputated. In spite of an endotracheal tube, excessive secretions accumulated, and it was difficult to maintain a clear airway during the operative procedure. In the immediate postoperative period, the patient was unresponsive and decerebrate. The left pupil dilated and became fixed to light. The blood pressure rose to 170/100, the pulse to 100 to 120, and the respirations to 30 per minute. The temperature remained between 103 and 105°F. by rectum. On June 29 the operative site was re-explored, and further internal decompression accomplished.

Fourteen days after this operation a secondary, mixed meningitis caused by an unidentified gram-negative rod and *Neisseria intracellularis* developed. This infection was controlled with antibiotics.

During the next 3 months, the patient remained unresponsive and decerebrate. Approximately 3½ months after the illness began, the cerebrospinal fluid was crystal clear and contained only 9 lymphocytes and 3 polymorphonuclear leukocytes per cubic millimeter. The total protein was 61 mg., and the sugar 42 mg. per 100 ml. About 4 months after the onset of the illness, the patient appeared to respond. He looked at the examiner and grasped with his right hand on verbal command. Within the next month these responses became definite and could be consistently obtained when he was awake. Throughout this period, he was on a Foster frame, which was turned at regular intervals. He was fed by gavage, and a free airway maintained by tracheotomy. Several pulmonary and urinary infections that were treated with appropriate antibiotics developed.

Five months after the onset of the disease, he was transferred to the Bronx Veterans Administration Hospital. On admission, the temperature was normal, and the pulse 90; the blood pressure was 130/90. He blinked in response to threatening stimuli and moved the right arm but not the left arm or either leg. He responded only to painful stimuli applied to the right side. There were bilateral Babinski signs.

On December 3 the lumbar puncture was repeated. The initial cerebrospinal fluid obtained was bloody, but this cleared rapidly and the supernatant fluid was not xanthochromic. Routine bacteriologic culture of the fluid was negative; it contained 6 leukocytes and 2200 erythrocytes per cubic millimeter. The total protein was 90 mg., and the sugar 40 mg. per 100 ml.

The tracheotomy opening was closed in March, 1954, and subsequently there was no respiratory embarrassment. Despite anticonvulsant medication the patient had recurring generalized seizures, which occurred in a flurry every few months. There was progressive improvement in his ability to speak though speech remained slurred. By October, 1954, he could answer questions appropriately, but vocabulary was limited to a few words. The last report in September, 1955, indicated that he had a severe degree of mental impairment. He was disoriented in time and place, with a digit-retention performance of 3 forward and 3 backward. He could count to 10 and add 2 and 2. He could not subtract 7 from 100 correctly. His general fund of information was markedly limited.

Recovery of motor function was slow but progressive. In October, 1954, he had limited movement of the right arm. This improved so that by September, 1955, there was moderately good though imperfect function in the right arm and some movement in the left hand. There was no return of motor function in the legs. Contractures developed but were treated surgically in anticipation of further recovery.*

Virologic Studies

No attempt at isolation of a virus was made during the first month of the illness. On the thirty-fifth day of the disease, cerebrospinal fluid was removed from the lumbar sac under sterile precautions and frozen rapidly with dry ice. It was shipped in this state by air to the Third Army Medical Laboratory, Atlanta, Georgia, where it was injected into the brains of adult and suckling mice. No sign of disease appeared in the animals within twenty-one days of inoculation, and the study was considered to be negative.

On the one hundred and thirty-sixth day of disease, when evidence of the acute infection had entirely subsided, cerebrospinal fluid from the lumbar sac and a biopsy of brain adjacent to that removed at the operation were injected into infant mice, adult mice and embryonated eggs at the Department of Virus and Rickettsial Diseases, Army Medical Service Graduate School, Washington, D. C. These specimens were obtained and handled as described above. No virus was isolated by these methods.

Table 1. *Serologic Studies for Herpes Simplex.*

Date of Serum	Day of Illness	Herpes-Simplex Complement-Fixation Test	Herpes-Simplex Neutralization Studies
7/6/53	15	Positive in 1:64 dilution*	Positive
8/4/53	44	Positive in 1:16 dilution*	Not done
8/24/53	65	Positive in 1:16 dilution*	Positive
11/12/53	144	Positive in 1:8 dilution	Not done
11/23/53	155	Positive in 1:16 dilution	Not done

*Results of 3 separate tests.

The results of the serologic studies for herpes simplex are outlined in Table 1. Neutralizing antibodies against herpes simplex were found in serums taken on the fifteenth and sixty-fifth day of the illness. Herpes-simplex complement-fixing antibodies were present in a dilution of 1:64 on the fifteenth day of the disease and, twenty-nine days later, were found in a dilution of 1:16. This represented a fourfold decrease. Low antibody titers of 1:16 and 1:8 were demonstrated subsequently on the sixty-fifth, one hundred and forty-fourth and one hundred and fifty-fifth days of the illness.

*Since this paper was submitted for publication, another article concerning the same patient has appeared.[20] No serologic data are presented, and since we believe that these data modify the conclusions to be reached from the study of this case, publication here is considered justified.

Neutralization studies for lymphocytic choriomeningitis, eastern equine encephalitis, western equine encephalitis and St. Louis encephalitis were negative. Complement-fixing antibodies for mumps were present in low dilutions in serums obtained on the fifteenth, forty-fourth, sixty-fifth, one hundred and forty-fourth and one hundred and fifty-fifth days of the illness. This was interpreted as indicating an old, rather than a recent, infection. Negative serologic studies for syphilis, typhoid, paratyphoid, infectious mononucleosis, brucellosis, tularemia and leptospirosis were obtained.

FIGURE 1. *Elliptical Area of Cortical Necrosis Containing Microglia, Histiocytes and Other Mononuclear Cells (Hematoxylin and Eosin Stain X68–AFIP Photograph 54-19,912). Note the relation of the necrosis to the small vessels, the perivascular cuffing and the mononuclear and hemorrhagic infiltration of leptomeninges.*

NEUROPATHOLOGICAL STUDY

As previously noted, the right temporal lobe was hemorrhagic, soft and mushy. Blocks of brain were embedded in paraffin, sectioned and stained with hematoxylin and eosin. Representative slides from the occipital and parietal areas were normal. However, several sections from the temporal lobe showed varying degrees of focal necrosis, softening, recent hemorrhage and infiltration of the perivascular and periadventitial spaces with mononuclear cells. The meninges overlying these cortical areas were infiltrated with moderate numbers of mononuclear cells and lesser numbers of polymorphonuclear leukocytes (Fig. 1).

The areas of softening were devoid of recognizable nerve cells, astrocytes and oligodendroglia. In these regions large numbers of compound granular corpuscles, other mononuclear cells and a few polymorphonuclear leukocytes were seen. The surrounding areas were diffusely infiltrated with microglia and activated astrocytes. The majority of nerve cells in these areas were either pyknotic or swollen. The damage was most severe in the cortex although the subjacent white matter was also involved. The meningitis was severest near the most diseased cortex. In some areas the leptomeninges appeared normal.

Inclusion-bearing cells were found in the vicinity of but not in the necrotized foci. The inclusions were seen most commonly in glial nuclei but were present also in occasional nerve cells. The identity of the involved glia was often difficult to ascertain. They usually resembled swollen oligodendroglia, but certain differentiation from astrocytes was frequently not possible. The inclusions were predominantly eosinophilic though many had a basophilic hue. Although usually solitary, some inclusions were multiple. Most inclusions were granular but a few were hyaline. In general, they occupied about half to three quarters of the nucleus. A halo surrounded most of the inclusions, and the chromatin was displaced to the periphery of the nucleus, where it formed a beaded, circular pattern on the nuclear membrane. Fine strands of chromatin extending as spokes in a wheel from inclusion to nuclear membrane were seen in many cells (Fig. 2).

DISCUSSION

This patient had a fulminating febrile illness, signs of meningeal irritation, delirium progressing to stupor, hemiparesis and choreoathetoid movements. The cerebrospinal fluid was bacteriologically sterile and contained about 500 cells per cubic millimeter, of which a third to a half were polymorphonuclear leukocytes. These findings with a normal cerebrospinal-fluid sugar excluded from serious consideration the usual pyogenic meningitides and suggested the possibility of some other type of intracranial suppurative infection such as acute brain abscess or subdural empyema. The roentgenographic findings of a displaced pineal gland lent support to this opinion, and a ventriculogram was taken. No subdural empyema was encountered, and the precraniotomy diagnosis was a right-temporal-lobe abscess.

There is a close similarity between the clinical features of the present case and of those previously reported cases of acute encephalitis with intranuclear inclusions.[15,17,18] On the other hand, despite the duration of illness, the findings presented here are to be contrasted with the clinical pattern observed in the majority of cases of subacute or chronic encephalitis

with intranuclear inclusions. In these, the onset has usually been insidious, with symptoms and signs of intellectual deterioration, disordered gait and myoclonic or generalized seizures. Fever and signs of meningeal irritation have been lacking, and the cerebrospinal fluid has rarely contained cellular elements even in the early phase of the illness; a first-zone colloidal-gold reaction has frequently been found. Generally, after an unrelenting course of many weeks, months or even years, these patients have become demented, blind, decorticate or decerebrate. Death has been caused, in most cases, by some intercurrent infection.

FIGURE 2. *Inclusions in Nerve Cells and Oligodendroglia (Hematoxylin and Eosin Stain X675–AFIP Photographs 54-19,914–19,917).*

Note the margination of the chromatin, relatively clear area surrounding the inclusions and the tendency for fine strands to extend from the inclusions to the nuclear membrane. Solitary and multiple inclusions are seen.

The present case is exceptional in that the patient survived the acute illness. We are inclined to attribute the nonfatal outcome to good nursing and supportive medical care rather than to a mild form of the disease. We also believe that the surgical decompression, by reducing the heightened intracranial pressure, probably contributed to survival during the acute phase of the illness.

The extent of disease in the present case is unknown. The choreoathetosis suggests involvement of structures from mesencephalic tegmentum to the basal ganglions, and the decerebration implicates, in general, the region of the upper midbrain or the subthalamic-thalamic region or both. The focal involvement of the right temporal lobe, with resultant edema sufficient to displace the pineal gland and to distort the ventricular pattern, is of interest. Displacement of the ventricular system has been demonstrated in a previous case,[18] but it is not at all clear to us why such asymmetrical involvement should occur. Striking involvement of the temporal lobe has also been described by Haymaker[15] in cases of herpes-simplex encephalitis that he studied. This was true even though in some cases changes were relatively mild in other cortical areas. In general it can be said that the available pathological findings in our case seem identical to those found in the previously reported cases of acute encephalitis with intranuclear inclusions, which include the proved cases of herpes-simplex encephalitis. On the other hand the changes found in the cases of subacute or chronic encephalitis with intranuclear inclusions differ from those reported here. Swelling and softening of the brain have been described only rarely whereas a firmer-than-normal texture reflecting considerable chronic gliosis of the cortex has usually been found. Some observers[11] have stated that the inclusions are more hyaline in the subacute and chronic cases, but Malamud, Haymaker and Pinkerton[6] have noted no essential differences.

Early recognition of the nature of the pathological findings in this case led to an intensive quest for an etiologic agent. All serologic tests were negative except for the herpes-simplex neutralization and complement-fixation tests. A significantly high level of complement-fixing antibody was found fifteen days after the onset of the illness, and a fourfold decrease in titer on the forty-fourth day (Table 1). Subsequent antibody titers were consistently low. Thus, a definite diagnosis cannot be made, for this requires the demonstration of an absent or low antibody titer during the first week of the illness and at least a fourfold increase later in the course of the disease.

Nevertheless, the finding of such a significant drop in antibody level is highly suggestive of a recent herpetic infection. Moreover, Gajdusek, Robbins and Robbins[21] recorded a titer of 1:64 as the maximal level obtained in the serums of 12 of 16 children with primary herpetic infections. Of course, the possibility of anamnestic complement-fixing antibody response cannot be definitely excluded in our case since neutralizing antibodies against a strain of herpes-simplex virus were present in serums obtained on the fifteenth and sixty-fifth days of the disease and must be in-

terpreted as simply confirmatory of a previous herpes-simplex infection, either recent or remote. The failure to isolate the virus from the brain on the one hundred and thirty-sixth day is not inconsistent with the diagnosis of herpes-simplex encephalitis, for the clinical and laboratory findings suggest that the infection was quiescent when recovery of the virus was attempted.

Of the previously reported cases of acute encephalitis with intranuclear inclusions, 4 have been proved examples of herpes-simplex encephalitis[12-15]; no attempt was made to establish a specific diagnosis in the 4 other cases, and the etiology of the disease in these cases remains unproved.[16-18] Until recently, repeated attempts to isolate a virus from the cases of subacute or chronic encephalitis with intranuclear inclusions have been unsuccessful. In 1953, however, a strain of herpes-simplex virus was recovered from the brain in a fatal case by Foley and Williams.[11] Negative complement-fixing antibody and neutralization tests for herpes simplex were obtained at an unstated time during the illness, which lasted for twenty-seven weeks. The recovered virus was considered to be a contaminant. Negative serologic tests for herpes simplex were obtained during life, and no virus was recovered after death in 2 other fatal cases studied. The illness in 1 of these patients lasted for six weeks; the other patient survived for seventeen and a half months. To our knowledge these are the first proved cases of subacute or chronic encephalitis with intranuclear inclusions in which serologic tests for herpes simplex have been employed. It is of interest, also, that the authors biopsied the brain in 1 of their cases, and, although a diagnosis of encephalitis was made by Dr. J. G. Greenfield, the specific intranuclear inclusions were not found until postmortem examination.

Until new facts are available, the etiology of most cases of "inclusion encephalitis" must be considered unknown. In the future, knowledge of the cause or causes of this disorder should be advanced by its earlier recognition in the clinic, with the subsequent application of more extensive serologic tests and virus-recovery procedures. In this regard, the clinical picture and electroencephalographic findings in the subacute and chronic cases are distinct enough so that in several cases the correct diagnosis has been made during life.[5,11]

Summary

A nonfatal case of acute encephalitis in which intranuclear cellular inclusions were found on biopsy of the brain is presented. Serial serologic tests suggested that the etiologic agent was the virus of herpes simplex. The case is considered in relation to the previously reported examples of encephalitis with intranuclear inclusions.

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MEDICAL PROGRESS

PROCTOLOGY (Concluded)

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PILONIDAL DISEASE

To anyone interested in the many theories of the origin of pilonidal cysts the article by Hopping[22] provides ready access to all of them. This research, based on 174 references and on microscopical examination of 133 specimens over a three-year period, with a study of 499 cases, including follow-up data, provides a worth-while source of information on this subject. In addition, Hopping praises the study of Kleckner in 1936, which was based on a composite study of 4000 cases of his own and others. Hopping's cases were treated by five different methods. Recurrence rates varied from 24 per cent in those closed with drainage to 4 per cent in those left wide open. The latter group included about 75 per cent of the cases.

Hopping mentions that he could find in the literature a report of only 1 case of cancer in association with pilonidal disease — a basal-cell epithelioma reported by Goldman and Kalow. In this connection the moment seems opportune to mention an unreported case of my own: that of a nineteen-year-old girl operated upon in 1939, with excision of cyst and sinuses as an open operation. I did not recognize a tumor while doing the operation, but the pathological report was returned as "pilonidal cyst and sinus–carcinoma of skin (mixed squamous and basal cell"). So far as I know there was no recurrence.

A new theory regarding the origin of pilonidal cysts and sinuses has been introduced by Brearley,[23] who has reviewed and discarded the several explanations based on the concept of a congenital origin and cites observations and theories in favor of an acquired origin. He believes that the external hairs in the intergluteal cleft are rolled together by the friction of the buttocks and that the points of these stiff hairs puncture the skin of the depth of the groove, which is made taut by the lateral pull of the buttocks when pressure is exerted as in sitting. After puncture by the free ends of hairs, still attached by their roots to adjacent skin, the hairs are loosened and sucked beneath the skin by the rolling motion of the skin of the buttocks in this area. Most common in swarthy males, who have more and stiffer hair, the condition occurs after puberty, and the incidence falls off sharply in middle age, when the hair softens. As a basis for this theory he made observations of hairs protruding from these sinuses and found the follicle end of the hairs to be on the outer rather than the inner end of these loose hairs. Also, in support of his theory, Brearley cites the occurrence of a somewhat similar situation occurring in barbers in the interdigital webs of their fingers.

DIVERTICULOSIS AND DIVERTICULITIS

There seems to be increasing interest in the effort to prove that diverticula of the colon may occasionally be a source of bleeding and even massive hemorrhage. Noer[24] has reported 2 cases of massive hemorrhage and has gone over carefully 18 reports in the literature, embracing 41 other cases since 1942. In addition, he reviewed 68 cases of diverticulitis and diverticulosis in Louisville General Hospital, 20 of which were associated with some rectal bleeding, and summarized 27 reports from the literature totaling 2896 cases, with visible blood in the stools in 11 per cent.

Noer cites his own evidence, from injection studies of blood vessels of the colon in several specimens, that the blood supply in and around diverticula is rich, and concludes that ulceration with hemorrhage is therefore entirely possible.

His 2 cases, nevertheless, lack absolute proof, as he himself admits. Both came to autopsy. In 1 the pathologist thought the blood originated above the colon, and in the other there were ulcers in stomach and duodenum.

Discussing this paper before the Southern Surgical Association, Rosser mentioned his review of 110 patients, 49 with diverticulitis and 61 with diverticulosis alone, bleeding being more common in the second group than in the first, a fact that Colcock also pointed out. Of these 110 cases carcinoma was found in 6, adenomas in 7, and other tumors in 2 — all likely sources of bleeding.

Perhaps the most convincing point in the discussion was that of McCutcheon, who mentioned 2 cases of massive hemorrhage in which a single diverticulum in the sigmoid appeared black and after resection of a segment of sigmoid in each case there was no recurrence of hemorrhage.

Rives also mentioned a study by Emmet, at New Orleans Charity Hospital, of 206 cases of massive bleeding in which duodenal ulcer was the source in 39 cases and diverticulosis thought to be the source in 33. He agreed with Rosser that it was not necessary for the diverticula to be inflamed to produce bleeding, and he also brought out the point that benign tumors of the bowel were a more frequent cause of massive bleeding than malignant tumors.

Another article, by Young and Howorth,[25] reports a single case of massive hemorrhage in which there

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were many diverticula in the colon but only 2 in the upper sigmoid and none in the lower. Resection of the last 5 cm. of ileum and the colon down to the low sigmoid was carried out, with ileosigmoidostomy. Sixteen transfusions were necessary. The pathologist found no polyps but a number of inverted diverticula, one of which was ulcerated, and there were large vessels under the ulcer.

The report does sound convincing so far as this one case is concerned, but I believe that the emphasis should still rest on the necessity of eliminating every other source of bleeding in the gastrointestinal tract before resting on a diagnosis of bleeding diverticula. The very simple procedure of injecting internal hemorrhoids once or twice, if present, will serve as a good therapeutic test of whether they are the source of excessive bleeding, which they occasionally are.

Colcock[26] describes 40 patients with diverticulitis operated upon at the Lahey Clinic in the years 1953-1956, supplementing his earlier report on 50 cases in the period 1948-1952.

A single-stage resection was carried out in 23 patients, colostomy and resection in 13, colostomy only in 2, colotomy in 1, and exploration alone in 1. There were no deaths.

Findings included some degree of perforation in 16 cases, polyps (1 malignant) in 4, and obstruction of the sigmoid in 3 and of the small bowel in 3. There were single cases of foreign body, scrotal abscess, carcinoma, and ulceration of the rectum. Of the 16 perforations 3 were into the bladder, 2 into the vagina, 2 into the ileum, and 1 to the skin. A total of 38 operations were necessary on the 16 patients with perforations.

Earlier resections for diverticulitis would prevent many of these complications and decrease morbidity.

Spontaneous Perforations of the Normal Colon

Eadie,[27] from Westminster Hospital in London, has found in the literature 4 cases of spontaneous perforation in a macroscopically normal pelvic colon and reports another case in this article. It occurred in a woman of fifty-seven while she was straining at stool. The perforation, as in the other 4 cases, was on the antimesenteric border of the pelvic colon, which in this case was loaded with hard feces, and there was no evidence of any inflammatory process adjacent. The affected loop was exteriorized, the colostomy closed six weeks later, and the patient continued well after four years, a subsequent barium-enema examination having been reported as negative.

The 4 patients previously described all survived their perforation and their surgery, 1 being treated by simple closure of the rent, 1 by closure and cecostomy, 1 by closure and a left-sided iliac colostomy, and the fourth by exteriorization. Eadie mentions 2 reported series of large-bowel perforations, 1 of 90 cases, all of which were associated with either neoplastic or inflammatory disease; in the other series of 136 cases only 1 occurred in normal bowel.

Adenomas (Mucous Polyps)

Numerous articles have been and will be written on the subject of benign adenomas of the colon and rectum and their role as precancerous lesions. It is not always clear in the minds of doctors that the white, fibrous polyps due to hypertrophy of anal papillae, which may protrude from the anus or be palpable just inside and are covered with squamous epithelium, are not premalignant lesions though often associated with an anal fissure.

Van Buskirk[28] reports 100 cases in which 216 polyps of the colon had been found and removed in the West Roxbury, Massachusetts, Veterans Administration Hospital. Polyps could be seen by sigmoidoscope in 78 of these, and were multiple in 35 of the 100. In 18 patients the polyps could be palpated in the rectum. In about a third of the cases diagnosis was made by barium-enema study. Bleeding had been noticed in 55 per cent, and 30 per cent had no symptoms.

Follow-up studies in 71 of the 100 resulted in the finding of additional polyps in 12 patients and carcinoma in 1 by combined sigmoidoscope and barium-enema examination, re-emphasizing how essential it is to keep such patients under observation at intervals of three months or so.

The development of carcinoma in adenomas of the colon or rectum is common enough, but unusual in a child of two, as reported by Schilla.[29] This polyp, 1.5 by 2.5 cm., had prolapsed through the anus, being attached by a short pedicle 8 cm. above the dentate line. Removal was simple, and a diagnosis of carcinoma in both pedicle and polyp was made by the hospital pathologist and confirmed by several others, after which abdominoperineal resection, with preservation of the anus, was carried out but no residual carcinoma was found in the resected rectum.

Since the child survived and had satisfactory bowel function the procedure seems to have been justified, in view of the involvement of the pedicle of the polyp. On the other hand the resection carried some risk in a two-year-old child; there proved to be no demonstrable residual cancer in the resected bowel, and the polyp was attached in an area that could have been kept under observation by palpation and proctoscopy fairly easily even though the exact site of attachment was hard to identify. The decision whether to resect the rectum with the risk involved in so young a child, or to observe the child with the risk of recurrence locally or elsewhere later when resection would be less favorable, must have been a difficult one to make. There is something to be said for both points of view.

The removal of benign adenomas by surgical excision, cold snare, fulguration or snare electrocoagula-

tion is a matter for the individual surgeon to decide, depending on his experience, his equipment and his conscience. It is possible to get into trouble with hemorrhage hard to control and with perforation if the lesion is high. Experience and care will avoid both.

An interesting suggestion by Rosenberg[30] to decrease the danger of too deep burning in electrosurgical removal of polyps of the rectum and sigmoid is the injection of a submucosal wheal of saline solution under the lesion before electrocoagulation. By the use of a long, 23-gauge needle he has carried out this procedure through a 24-cm. sigmoidoscope, with no ill effects.

Before using this technic on patients he had produced varying degrees of burns in bowel segments after removal for other lesions, and found a definite protection of the muscular layer in the submucosally injected specimens as compared with those not injected.

This procedure, though not really necessary in pedunculated lesions, might permit a more thorough removal of a flat lesion. On the other hand there is more need, in a flat lesion, of complete surgical removal, or of simple biopsy without electrosurgical destruction, for purposes of careful pathological evaluation.

Familial Multiple Polyposis

Lockhart-Mummery, Dukes and Bussey[31] report the experience of St. Mark's Hospital, London, in an extensive review of familial polyposis in which 1069 members of 58 families have been traced. This group includes 218 with polyposis, in 154 of whom cancer developed.

Polyps appear in childhood or early adult life, and the average age at onset of symptoms in this group was twenty. Cancer is likely to appear about fifteen years after onset of symptoms, or at the age of thirty-five. Males and females are about equally affected.

Sixty cases between 1918 and 1954, treated surgically, are divided for comparison of methods into a group of 21 in the years 1918-1945 and 39 from 1946 to 1954. The former group, in which only 4 were treated by subtotal colectomy and an anastomosis of the ileum to the rectum or sigmoid, carried a 23 per cent mortality for the 21 cases, 17 being treated by something less than a subtotal resection. None received an ileostomy.

In the second group of 39 cases, 29 had a subtotal colectomy with anastomosis of the ileum to a rectal stump, usually about 12 cm. from the anus, and in 2 others the ileum was brought down to the anus. In 5 cases total proctocolectomy with ileostomy was done. Less radical resections were carried out in only 3 of the 39 cases in which the presence of cancer and metastases precluded any chance of cure by a more radical method.

Of the 29 patients in the second group who had subtotal colectomy with ileorectal or sigmoidal anastomosis, 26 are alive and well.

Observation of the residual rectum and colon at intervals of every three months, or oftener at first, is important to permit fulguration of polyps that may recur after the original ones in this lower segment have been cleaned out.

Smith and Jackman,[32] at the Mayo Clinic, reviewed 96 cases of multiple polyposis, of which 92 were familial, over a twenty-one-year period, 1933-1953 inclusive.

The group consisted of all patients treated by colectomy with preservation of a terminal segment of rectum and includes practically all the patients ever treated by this method at the Clinic.

There were 10 hospital deaths. Of only 13 patients operated on before 1940, 7 died. Of the 6 who left the hospital, carcinoma later developed in the rectal segment in 2.

Since 1940 there have been only 3 hospital deaths in 83 patients operated upon by this method.

The 96 patients consisted of 50 males and 46 females, 10 of whom were under twenty, sixty-two between twenty and forty and 24 over forty years of age. Frank carcinoma proximal to the terminal segment was present in 30 patients as proved at operation.

Follow-up data in this group of 96 patients are therefore based on 86 who survived the operation. Many polyps were subsequently fulgurated in the terminal segment of colon. Of 40 patients followed for over two years carcinoma developed in the terminal segment in 6 patients and more than one carcinoma developed in 5 of these.

Peutz–Jeghers Syndrome

A syndrome in which the presence of melanotic spots on the lips or buccal mucosa is associated with the presence of polyps somewhere in the gastrointestinal tract was reported by Peutz, of Holland, in 1921 and emphasized in a review by Jeghers et al. in 1949. The syndrome is considered to be based on an inherited mendelian dominant and occurs usually in brunettes with brown or dark-blue eyes. The spots vary from a light tan to pale blue and are 1 to over 5 mm. in diameter and numerous.

Berkowitz, Pearl and Shapiro[33] report 3 additional cases, which they say raises the total of reported cases to 37, with malignant changes in 9 of these. Polyps occurred in the large bowel in 10 cases, stomach in 10, duodenum in 4, jejunum in 19, ileum in 15 and unspecified areas of small bowel in 8.

Another report on the same subject by Pool, Guice and Farringer[34] adds 2 patients, aged thirteen and four years of age, both members of a single Negro family in which the father and 4 children had the spots on the buccal mucosa.

The importance of these pigmented spots lies chiefly in the fact that a search for polyps should be made in people who have them. They are considered unrelated except as being in each case a manifestation of the same dominant mendelian factor in that individual.

Freeman and Ravdin[35] report still another case in which the polyps were confined to the ileum, and they make mention of at least 18 articles on this subject between January, 1953, and May, 1955. Anemia is present in about 70 per cent; the family history is positive in about 70 per cent, and malignant changes had occurred in 17 per cent of 40 patients in collected reports.

Crumpacker[36] also added a case from the Greenbrier Clinic in a woman of thirty-nine with a 3-mm. melanotic spot on the vermilion surface of the lower lip, "not obscured by a generous application of lipstick." There were no gastrointestinal symptoms except occasional mild right-lower-quadrant discomfort and 1 fairly severe right-upper-quadrant attack. The family history disclosed that the patient's mother and 3 of her mother's brothers and sisters and 2 uncles had died of intestinal cancer. Proctoscopy showed several rectal polyps, but no certain ones were revealed by barium-enema study. Subsequently, a total of 14 nonmalignant, small polyps were found in the rectum and sigmoid and fulgurated.

Of further interest in connection with multiple polyposis is an article by Weiner and Cooper[37] describing 4 brothers, all of whom had multiple polyposis, associated with multiple cutaneous and subcutaneous tumors and osteomas in 3, but with only osteomas evident in the fourth. Carcinoma also developed in 3.

This article, on a syndrome first described by Gardner in 1951, was also commented upon in the editorial column of the *New England Journal of Medicine* in the same issue.

Cancer

Cytology

Galambos and Klayman[38] report their experience in the diagnosis of malignant tumors of the colon by exfoliative cytology over a period of eighteen months. Colonic washings were given in 68 patients, using Ringer's solution in 20 and Ringer's solution followed by 500 to 1000 ml. of acetate buffer with 14 to 21 mg. of salt-free chymotrypsin, retained for five to ten minutes, in 48 patients. After gross feces were filtered out, the fluid was collected in iced containers and centrifuged at 5000 r.p.m., and the sediment smeared on slides thinly coated with Mayer's albumin.

A correct diagnosis was made in 16 of 26 patients who had cancer. Of the 68 patients tested 32 were definitely proved subsequently, by surgery or observation, not to have had cancer, and in this group no cells thought to be malignant were recovered. The second method of washing, used in 48 patients, yielded a much higher percentage of positive findings.

Ascending Colon

Griffin, Judd and Gage[39] present some Mayo Clinic figures on survival rates after resections of the ascending colon for cancer. A prior report by Mayo and Lovelace of cases treated between 1907 and 1938 had shown a five-year survival rate of 57 per cent. This era saw the evolution of procedures culminating in the one-stage resection with ileocolostomy, and also was the preantibiotic era.

The present review embraces cases treated between 1939 and 1948 when the rate of "curative" resections was 70.3 per cent and the hospital mortality 6.5 per cent. The five-year survival rate was 60.4 per cent among patients surviving the operation. Operability, however, had risen to 77.1 per cent in this period and up to 85.9 per cent in 1952, with increasing use of palliative resection.

Rectum and Sigmoid

Somewhat similar statistics from the Mayo Clinic are presented by Waugh, Block and Gage[40] regarding carcinoma of the rectum and sigmoid. Their study is based on 625 patients treated in the period 1941-1950, but especially on 444 of these in whom the lesion was located at or more than 15 cm. below the anal margin.

The mortality in the 444 cases was 3.8 per cent.

Survival rates for five years were as follows: anterior resection, 65.6 per cent; sphincter-preserving procedures, 53 per cent; and combined abdominoperineal resection, 51.6 per cent.

Mayo and Fly,[41] at the Mayo Clinic, have also made a recent analysis of 1146 patients operated upon for carcinoma of the rectum and sigmoid in the years 1945-1949 inclusive. Presumably, this series included the patients of the last five years in the previous report. There were 717 men and 429 women. Metastases to lymph nodes were present in 45 to 50 per cent of cases. The over-all five-year survival rate was 52.5 per cent. Procedures used were anterior resection in 319 patients, combined one-stage abdominoperineal resection with colostomy in 612 and a two-stage posterior resection in 215; survival statistics are included regarding level of lesion, age, sex, metastasis and grade of malignancy as they varied in the three operative groups. The chief conclusion was that in lesions lying between 6 and 15 cm. from the dentate margin the cure results were as good in sphincter-preserving operations as in the excisions with colostomy.

Recurrent Carcinoma after Continuity-Preservation Operations

Black and Kelly[42] (Mayo Clinic) report results of treatment in 116 cases of recurrent cancer after either segmental resections or the pull-through procedure. In 12 of the 116 cases no treatment of the recurrence was carried out. Of the remaining 104 a further re-

section in 12, with removal of all gross evidence of recurrence, resulted in 1 hospital death, 2 patients alive without evident disease seven and eight and a half years later, and 1 who died of recurrent disease after five years. Of the other 8, 1 died in a year, 5 within three years, and 2 within four years. Exploration without resection was done in 13. Palliative resection was carried out on 5 patients, and local excision in 4, whereas 70 were treated by irradiation, of whom 4 were apparently cured at five years, and 9 others survived for more than two years.

Uncommon Malignant Tumors

In the 1954 Medical Progress report on proctology in this journal mention was made of certain uncommon malignant tumors of the anus and rectum — cylindroma, carcinoid, melanoma, adenoacanthoma and Paget's disease of the anus.

Basal-Cell Carcinoma on a Fistula

Manheim and Alexander[43] report a case of basal-cell carcinoma of the perianal area surrounding the external opening of a fistula that had existed for twenty years. A wide local excision of this nickel-sized lesion of the skin, together with the fistula and a segment of underlying muscle, resulted in an apparent cure when the patient was seen four years later. There was no evidence of any tumor within the rectum so that the skin involvement, centering as it did on the external opening of the fistula, seems to have been a definite case of malignant degeneration based on the chronic inflammatory outlet of a fistula.

The authors included in table form a synopsis of 11 cases previously reported by several authors and present their own as the twelfth case in the literature.

Basal-Cell Carcinoma of the Rectum

Burns[44] reports a case of basal-cell carcinoma of the rectum — the first ever reported in the literature, he states. This tumor is reported occasionally at the anal outlet.

The growth, in Burns's patient, was an ulcerated lesion 4 or 5 cm. in size with an ulcerated crater 3.5 by 5.5 cm. There were metastases to four lymph nodes.

Epidermoid Carcinoma

Griffin[45] reported to the American Proctologic Society 7 cases of epidermoid carcinoma of the anus or rectum in a series of 103 cases of malignant tumors of the colon and rectum.

From Memorial Hospital in New York Stearns[46] provides a study of epidermoid carcinoma of the anus with particular regard to the handling of inguinal-lymph-node metastases, which occur in various reported series in 8 to 33 per cent of cases.

Stearns has reviewed 69 cases on which this report is based. Of these, 40 patients had no clinical evidence of groin involvement; in the other 29 there were 16 who had obvious metastases on admission to the hospital, and 13 in whom they appeared later, in 11 within two years.

On the basis of the pathologist's study of these specimens the spread was thought to have occurred by two routes: one directly to the superficial inguinal and thence to the deep iliac and obturator nodes, and the other by way of the internal iliac or obturator lymph nodes and thence to the superficial lymph nodes in the groin.

Survival rates with groin metastases were 16 per cent for three years and 12.5 per cent for five years. Of 17 patients on whom groin dissections were performed 9 died of disease within three years, 2 after five years, and 1 of other causes, and 5 are living free of disease two to six years later. But none who had clinical metastases on admission are alive.

Treatment of the primary lesions before or after admission varied from local excision to abdominoperineal resection, and a study of the tables will clarify these details.

It is the authors' belief that the additional salvage of patients by routine prophylactic, bilateral, deep and superficial groin dissection in all patients, with the risks and the unpleasant results of these procedures so far as lymphedema and so forth are concerned, is not enough to justify the prophylactic procedure as compared with its performance when lymph nodes develop.

Bowen's Disease

Grodsky[47] reported 3 cases of Bowen's disease (squamous-cell carcinoma in situ) of the anal region.

Leiomyosarcoma

Rebell and Hiatt[48] report a case of leiomyosarcoma of the rectovaginal septum, in which there was repeated, severe bleeding by rectum, treated by abdominoperineal resection.

Benign Tumors and Cysts

Laird[49] discusses presacral cysts and tumors in which he reviewed the report (1953) by Mayo, Baker and Smith, from the Mayo Clinic, of 161 cases and added 7 cases of his own, all cysts, and in all of which a connection with the posterior anal canal below the dentate line could be demonstrated.

Cox[50] reports another hidradenoma of the perianal area.

Oleomas

Lipoid granulomas (oleomas) of the rectum have been described by various authors as an occasional complication of the injection treatment of hemorrhoids with oil-base sclerosing agents. Wittoesch et al.,[51] at the Mayo Clinic, gathered 23 cases from records of patients between 1941 and 1954. In 12 of these there was a definite history of previous injection therapy, and in 6 there was uncertainty; in 5 no injections had been given, but they had undergone hemorrhoidectomy.

These nodules lay between 3 and 8 cm. from the anus in 21 patients and 12 and 15 cm. in 2 patients. In the recently injected cases tubercles and foreign-body giant cells were seen, and in those with a longer history much fibrosis had set in.

The diagnosis is established by the finding of numerous oil droplets in the microscopical sections after removal, but oleoma may be suspected when smooth submucous nodules are found in the lower rectum, usually covered with normal or slightly reddened mucosa. They must be differentiated from submucous abscesses, carcinoids, lymphomas, nodules of the prostate and vesicles, and presacral cysts. A history of injections, of course, is helpful.

Surgical excision can be easily performed, though the nodules may have been present for a long time with slight symptoms or none. I have recently removed one in association with hemorrhoidectomy in a man who had never received treatments nor had any previous operation in that area. He had used, on two occasions, the so-called "Preparation H," which has an oil base.

Amebic Granuloma

Spicknall and Peirce[52] provide an extensive review of the subject of amebic granuloma, with 125 references and a report of 4 cases seen among 214 patients with amebic colitis. Three of these were in the cecum, and 1 in the rectum.

The incidence of these lesions, which may be localized or more widely spread, is less than that of amebic hepatitis and abscess. These lesions simulate carcinomas and other inflammatory lesions, and their diagnosis rests on either biopsy or their response to antiamebic therapy. They will usually disappear after a month of treatment.

Megacolon

Swenson, Fisher and MacMahon[53] describe the indications for, and the technic of, rectal biopsy to establish or exclude the presence of true Hirschsprung's disease by the absence or presence of ganglion cells between the circular and longitudinal muscle layers of the lower rectum and upper anal canal.

Biopsy is useful when the clinical diagnosis is uncertain, as in the following circumstances: in patients whose colon has become contracted because of a previously established colostomy; in babies who are not yet old enough for the bowel to dilate; in patients with only a short segment of distal colon involved; and in patients having unusual symptoms of colonic dysfunction without chronic constipation.

Biopsy is obtained under general anesthesia by excision of a segment of internal sphincter, 5 to 10 mm., through a 1-cm. incision in the anal canal.

The procedure has been carried out in 40 patients, and on 10 cadavers with normal colons. In 19 patients, later proved to have Hirschsprung's disease by study of the resected colon, there were no ganglion cells in the biopsied specimens. In another 21, suspected of having Hirschsprung's disease, biopsies showed ganglion cells to be present, thereby ruling out congenital megacolon; treatment of the latter group by conservative measures confirmed the diagnosis of simple constipation.

Swenson and Fisher, in another article, have discussed the presence of megaloureter in 60 patients, half of whom had aparasympathetic bladders, and in a fifth of this latter group congenital megacolon was also present.

Pneumatosis Cystoides of the Intestine

Kreeger and Littman[54] reported the confirmatory diagnosis by biopsy through a sigmoidoscope in a case of pneumatosis cystoides intestinorum (gas-filled cysts of the intestinal wall), a rare condition first described by Bang in 1876. Barium-enema study had shown characteristic multiple, air-filled, round, filling defects in the wall of the sigmoid that narrowed its lumen. These cysts, lined with cuboidal epithelium, may be submucosal or subserosal, producing alternating constipation and diarrhea. They are of undetermined origin.

A paper on this subject, given recently at the meeting of the American Proctologic Society, added 2 cases to the total of around 250 reported in the literature since 1876. I have personally never seen a case.

Olson[55] has seen one involving the terminal ileum in an eight-year-old girl, with partial obstruction of the third portion of the duodenum by kinking.

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MEDICAL INTELLIGENCE

A CONSIDERATION OF CHILDBIRTH PROGRAMS*

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IN spite of the claims of some magazine writers, the idea of preparing expectant mothers for childbirth is not new. The present emphasis on preparation programs is a matter of evolution, not revolution. As early as 1773 Charles White, of Manchester, in his book, *The Management of Pregnant and Lying-in Women,* gave specific directions for supervision during pregnancy, for aiding the woman in labor and for making her comfortable afterward by letting fresh air and sunshine into her room and making it cheerful. Early in this century, when systematic prenatal care was being established generally, J. W. Ballantyne, of Edinburgh, suggested prematernity hospital beds and rest homes where maternity hygiene and "mothercraft" could be taught.

The present-day emphasis on preparing women for childbirth and giving them individual support and attention during labor also has its roots deep in the kind of obstetric care that a woman received when delivery was carried out at home, where her relations to her baby, her family and her surroundings were natural enough. She was not disturbed by white walls and people strange to her, wearing white uniforms and face masks. The help that she received from her doctor and nurse was intimate and individual, for she had her own doctor and nurse all the way through.

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It was inevitable that a great deal of this atmosphere would be lost when hospital deliveries became the rule, for efficiency in institutional management often has to sacrifice certain needs of the individual for those of the many. Hospital administrators have their problems too.

The problem of pain in labor is one of antiquity. In American obstetric tradition it is interesting to recall that when Walter Channing, of Boston, wrote his *Treatise on Etherization in Childbirth,* among his most powerful opponents were eminent members of his own profession who maintained that pain in labor was desirable and a natural manifestation of life force. At the same time, religious objections, urged for the most part by the clergy, were based chiefly upon what was said to be the primeval curse laid upon women in *Genesis* (3:16): "in sorrow, thou shalt bring forth children." It is incongruous for anyone to suggest that childbirth preparation programs are emphasizing a return to the days before Channing and Simpson. It is fair, however, to ask what is going on and how such programs came about. There is no doubt that thus far, along with much enthusiasm, they have stimulated a considerable amount of criticism and skepticism. A unique circumstance is the fact that the controversy is not confined to medical circles but finds influential participants outside that group in writers for popular magazines and others. A disturbing result of all this talk has been that the subject is often referred to as a new kind of obstetrics but recently discovered. It is true that within the last decade sharp attention was called to certain psychologic aspects of labor and delivery by the writings of Grantly Dick Read and Helen Heardman, of England, but the principles that they so forcefully emphasized are not basically different from those practiced by obstetricians of an older generation who delivered women in their homes.

The advent of the books of these two writers gave a powerful impetus to modern childbirth programs, in which the most important aspect is adequate and understanding support in labor and delivery. Neither of these writers appears to have advocated husbands in the labor room, rooming-in, combined classes for mothers and fathers and other innovations now associated with childbirth programs. Nor have these and

other chief writers on the subject suggested that anesthetic aids should not be used. Dick Read says:

> If there is true pain, anesthetics or analgesics should be exhibited at once, but absence of pain is the great contra-indication to the use of anesthetics and analgesics . . .[1] The administration of anesthetics and analgesics should have definite indication in obstetrics as it has in every branch of medicine or surgery. Pain is the only justification; it does not matter whether the pain is secondary to fear or whether it is primarily physical.[2]

The use of the term "natural childbirth" is unfortunate in many ways, for it suggests to many a synonymity with primitive and, at the same time, easy childbirth. Anyone familiar with anthropologic reports is quite aware that primitive women are not free from abnormal labors and excessive pain and that they are often subjected to practices reminiscent of the medieval torture chamber.

Another unfortunate circumstance has been the overemphasis of some enthusiastic proponents of natural childbirth on the psychologic importance of a spontaneous and a conscious delivery. The result has been that in many cases a "prepared" woman intent on such a delivery who finds herself in need of artificial help and complete anesthesia may come to think of herself as a failure and as wanting in strength of character. Common sense dictates that trainees in preparation programs be made thoroughly aware that such training is no panacea for short and easy labors and that its chief values lie in enabling a woman to understand herself better, to help herself in labor better, and to increase her own self-confidence. The woman who volunteers for such instruction should be fully told about the use of anesthetic aids and also that stoicism in itself serves no useful purpose. She should be told that pain is an individual response and that if she requires artificial aid, the circumstance is not to be interpreted by her as an assault upon her integrity as a person. With this kind of indoctrination there is no reason why the psychologic satisfactions of the woman who requires such aid should be radically different from those of a woman whose infant is delivered spontaneously after an easy labor.

It is generally admitted that the development of childbirth programs has been instrumental in bringing innovation into hospital obstetrics: rooming-in; emphasis on individual support during labor; husbands with wives during the labor period; and an increased interest and knowledge on the part of the parturient woman in the labor process. None of these things are incompatible with sound obstetrics, and they do have virtue in emphasizing the value of individual parturient care.

The term "childbirth program" is broader and better than that of "preparation program." Under the more inclusive term such practices as rooming-in can be included. Such childbirth programs obviously will vary in content from institution to institution where physical limitations may prevent some aspects from being put into operation. Obstetricians will agree, however, that co-ordinated and skillful labor support should be a part of every obstetric regimen everywhere.

One criticism that has been made of childbirth programs is that statistics proving their worth have been too scarce. This is true, but it must be recognized that many important values cannot be readily assessed by the usual methods. There are, nevertheless, studies that deserve attention such as Heardman's[3] report of 1000 primigravidas and the study of Thoms and Karlovsky[4] of 2000 consecutively delivered women (702 primigravidas). The former study included 500 controls delivered in separate institutions. The second study was made of women delivered in one institution. In Heardman's prepared women (500) the labor averaged three hours shorter than that in the unprepared group, and instrumental deliveries were about half as frequent. In the study of Thoms and Karlovsky the average labor for the multigravidas was approximately eight hours, and that for primigravidas fourteen hours, and delivery was accomplished in 49 per cent of the latter in less than ten hours. Other impressive observations in this report included lessened blood loss, lessened amounts of drugs and anesthetics and greatly lessened necessity for infant resuscitation. These authors state that the key to success in any childbirth program is skilled and sympathetic attendance for the woman in active labor; their 2000 mothers received this kind of labor support although the majority did not experience the full preparation regimen. The relatively shortened length of labors in these women, both multigravidas and primigravidas, emphasizes Eastman's[5] pronouncement, "the most common cause of uterine inertia in modern obstetrics is the premature and injudicious administration of analgesic drugs and conduction anesthesia."

It seems trite to say that the chief guiding influence in such childbirth programs must remain in the hands of doctors and nurses, but it is obvious that lack of interest or passive action on their part can be misinterpreted and harm public relations. What is needed is a more concerted action on their part toward the establishment of better obstetric care generally. The leaders in these groups must be more definite in their opinion about what constitutes obstetric care of high quality. Significant guidance for such an approach is offered in Eastman's[6] statement, "Natural Childbirth is a broad concept and represents an attempt on the part of those who care for pregnant and parturient women to understand the physiology of pregnancy and labor, especially in its emotional aspects, so that these important functions may be viewed with less apprehension and better understanding by patients and that greater skill in caring for them may be developed."

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DOCTORS AFIELD

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FEW people know about the origin of military signaling in the United States, on which so much depends, especially in time of war.

The use of a simple system of visual signals for the transmission of important news between neighboring cities was known to the ancient Greeks. A code described by the historian Polybius (204-122 B.C.) enabled each letter of the Greek alphabet to be signaled by means of the display of a certain number of lights to the right and left of a fixed central position. Although instances of the transmission for warning messages by lights and other visual signals can be found throughout history and the use of visual codes between ships at sea has been practiced by mariners for several centuries, down to the middle of the nineteenth century surprisingly little progress had been made in developing methods and instruments for the systematic exchange of military information by means of signals.

The construction of a practical working telegraph by Morse, in 1832-35, served to turn men's minds to the general subject of the interchange of ideas by signals, and in the years immediately preceding the Civil War the first steps were taken to introduce a method of signaling into general use in the United States Army. It is of interest that this first practical method of field signaling was developed by a doctor afield.

Albert J. Myer was born at Newburgh, New York, on September 20, 1827. After an apprenticeship as a telegraph operator he entered Hobart College, Geneva, New York, from which he graduated in 1847. From early youth he had exhibited a predilection for artistic and scientific studies, and upon leaving Hobart he entered Buffalo Medical College, from which, four years later, he received the degree of M.D. It was said of him "that he was specially noted for the manner in which he could take hold of an idea or principle, and, following it to its length and breadth, develop all there was in it or of it." His graduation thesis, "A Sign Language for Deaf Mutes," contained the germ of his visual signaling system.

After practicing medicine for three years he was commissioned in 1854 an assistant surgeon in the Regular Army and ordered to New Mexico for station. His attention had previously been directed to the desirability of devising a simple system of visual communication, and during his leisure hours at his isolated post he devoted himself to its development. In 1856 he drafted a memorandum on a new system of signals and obtained patent letters on it. Two years later the War Department recognized the possibilities of his proposed system by appointing a board to examine "the principles and plans of the signaling, mode of use in the field, and course to be pursued in introducing to the Army." One of Myer's assistants in demonstrating his system to the board was Lieutenant E. P. Alexander, Corps of Engineers, who, on the outbreak of the Civil War, organized the Confederate Signal Corps. For three months they experimented with flags, torches and glasses between Fort Hamilton, New York, and Sandy Hook, New Jersey, and in January, 1860, reported to the War Department what has since been known as the "wig-wag" system. In his annual report for 1859, Secretary of War Floyd commended Surgeon Myer's system to Congress, and as a result an initial appropriation of $2,000 was made "for the manufacture or purchase of apparatus and equipment for field signaling." The same act authorized the appointment on the staff of the Army of one signal officer with the rank, pay and allowances of a major of cavalry. Pursuant to this authority, the following appeared in General Orders No. 17, July 2, 1860:

> Signal Department,
> Assistant Surgeon Albert J. Myer to be Signal Officer, with the rank of Major, June 27, 1860, to fill an original vacancy.

Two weeks later Major Myer was ordered to report to the commanding general, Department of New Mexico, for duty. The War Department also directed that two officers be detailed for signal duty as his assistants. A campaign against hostile Navajos was being planned. During the campaign, which lasted several months, an extensive test of this new system, using both flag and torch, was conducted. The first type of flag was of a solid-white color, although the use of a black diagonal to distinguish it from a flag of truce was suggested. At the conclusion of the Navajo expedition the department commander, Colonel Fauntleroy, stated, "the services of the signal party have been valuable in the operations against the Navajos and have conclusively demonstrated not only the practical usefulness of field signals, but that they can be used under any of the contingencies of frontier warfare." It is also interesting that Lieutenant J. E. B. Stuart, later famous as a Confederate cavalry leader, tendered his services in October, 1860, to aid in this signal instruction.

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CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 42441

PRESENTATION OF CASE

A fifty-six-year-old man entered the hospital because of painful swellings of both hips.

Thirty-two years previously he began to have intermittent episodes of abdominal pain in the right upper quadrant that were associated with nausea and vomiting and relieved by milk and antacids. An appendectomy was performed six years later. About eight years before admission lysis of an adhesive band that had caused intestinal obstruction was performed at another hospital. Seven years before entry, after an injury, he became aware of a persistent mass in the right elbow. At about the same time a slightly tender, slowly enlarging, subcutaneous swelling below the left iliac crest was noted. Subsequently, a similar swelling appeared below the right iliac crest. He experienced dysuria, polyuria and nocturia over a period of six months. Because of worsening of the abdominal pain he was admitted to another hospital seven years before entry. The hemoglobin was 9.6 gm. per 100 ml. The serum nonprotein nitrogen was 130 mg., the total protein 7.6 gm., the albumin 5.4 gm., the globulin 2.2 gm., the bilirubin 0.3 mg., the calcium 9.6 mg., and the phosphorus 6.4 mg. per 100 ml. The chloride was 91 milliequiv. per liter. The carbon dioxide was 57 vol. per cent. Cephalin flocculation was ++. The thymol turbidity was 1 to 3 units. A phenolsulfonphthalein test showed 8 per cent excretion in two hours. A stool specimen gave a negative guaiac test. An upper gastrointestinal series demonstrated an ulcer on the posterior wall of the duodenum. With an ulcer regimen there was a temporary remission of symptoms. Intermittent claudication was noted during the five years before admission. Four years later, because of recurrence of the abdominal pain, a gastroenterostomy was performed at another hospital. During the two or three years before entry there was some urinary frequency and nocturia, with occasional burning on urination. One and a half years before admission he was hospitalized because of a massive gastrointestinal hemorrhage that was said to have been caused by a marginal ulcer. He was transfused with 9 units of blood and started on a regimen that included 1 or 2 quarts of milk and a half to a pint of cream daily, as well as Amphojel and Zymacap capsules. Because of persistence of mild abdominal pain he also took "soda" from time to time. During the three or four months before admission the lesions below the iliac crests and in the right elbow increased rapidly in size and became painful. At the same time he noted swellings in the right axilla and groin. There was a past history of excessive alcohol intake.

Physical examination showed a thin, pale man in no acute distress. Ophthalmologic examination revealed a distinct white deposit in the paralimbal regions of both corneas in the palpebral fissures; there were also crystals in the adjacent conjunctivas. There was gynecomastia on the left. A firm, movable, finely nodular, tender, subcutaneous mass that measured 4 cm. in diameter was palpable in the region of the right olecranon. Three firm, matted lymph nodes, each measuring 2 or 3 cm. in diameter, were felt in the right axilla. Similar nodes were present in the right inguinal region. Hard, slightly tender, fixed subcutaneous masses that extended from just below the iliac crest to the mid-thigh involved both hips. The heart was not enlarged. The edge of the liver was felt 3 fingerbreadths below the right costal margin. The spleen was palpable 2 fingerbreadths below the left costal margin. The right femoral pulse was weak; the left was absent. Pulses were absent in both legs.

The temperature was 98.8°F., the pulse 108, and the respirations 28. The blood pressure was 170 systolic, 112 diastolic.

The urine gave a + test for albumin; the specific gravity was 1.012; the sediment contained an occasional granular cast; a culture grew out a few beta-hemolytic streptococci. The twenty-four-hour urinary excretion of calcium ranged between 3.5 mg. and 8 mg., the phosphorus between 29 mg. and 138 mg., and the uric acid between 13 mg. and 35 mg. per 100 ml. A phenolsulfonphthalein test showed 5 per cent excretion after two hours. Examination of the blood revealed a hemoglobin of 7.8 gm. per 100 ml. and a white-cell count of 6700. The reticulocyte count was 2.1 per cent. A biopsy specimen of the bone marrow showed slight erythroid hyperplasia; there was no evidence of bone disease; a culture of the marrow was negative for tuberculosis. The nonprotein nitrogen was 59 mg., the calcium 12 mg., the phosphorus 5.6 mg., the uric acid 6.5 mg., the total protein 6.6 gm., and the iron 78 microgm. per 100 ml. The serum electrophoretic pattern was normal. The alkaline phosphatase was 2.2 units, the cephalin flocculation ++, the thymol turbidity 3.5

units, and the bromsulfalein retention 2 per cent. The tuberculin skin test was positive (O.T. 1:1000). Numerous stool specimens gave negative guaiac tests. An x-ray film of the right elbow demonstrated a nodular calcification (Fig. 1), measuring 4.5 by 2 cm., in the region of the olecranon bursa; calcification in an artery in the arm was noted. An abdominal film showed large nodular masses of irregularly calcified material overlying both hip joints (Fig. 2); the spleen was enlarged, and the kidneys were decreased in size. Skeletal films showed a large mass in the right axilla similar to those described in the

FIGURE 1. *Film of the Right Elbow.*
There are calcareous deposits in the soft tissue opposite the olecranon process.

hips (Fig. 3); calcification of the space between the eighth and ninth thoracic vertebras was seen; an area of calcification in the left leaf of the diaphragm was noted; the abdominal aorta and the left iliac artery were markedly calcified. A film of the chest after a barium swallow was normal. An upper gastrointestinal series demonstrated no obstruction or marginal ulcer at the site of the gastroenterostomy; a small ulcer crater was found along the greater curvature of the duodenal bulb. An upper gastrointestinal series two weeks later revealed an active ulcer crater that measured slightly less than 1 cm. in maximum dimension, projecting from the distal loop of the jejunum about 3 cm. from the gastroenterostomy; the duodenal bulb was not adequately visualized. An electrocardiogram showed a sinus tachycardia at a rate of 105 with normal PR and QRS intervals; Q waves of probably abnormal size were seen in Leads 2, 3 and aVF; the T waves were slightly low in the limb leads and upright in Leads V_1, V_2 and V_3; the R waves were tall in Leads V_4 and V_5.

A biopsy specimen of the mass in the right elbow showed metastatic calcification with a foreign-body reaction; a culture showed no growth; smears and a

FIGURE 2. *Film of the Hips.*
Note the extensive deposition of homogeneous calcification in the soft tissue about both hips.

culture for acid-fast bacilli were negative. The administration of sodium phytate and EDTA was without effect on the clinical course. The serum calcium ranged between 8.6 mg. and 14 mg. per 100 ml., with most of the values between 12 mg. and 14 mg. per

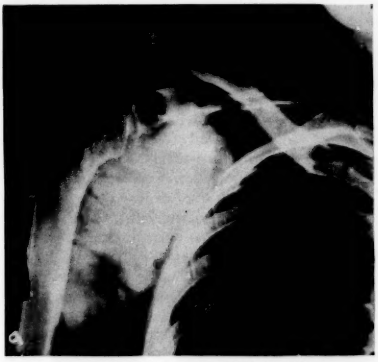

FIGURE 3. *Film of the Right Shoulder.*
There are large, calcified masses in the soft tissues of the axilla.

100 ml., the phosphorus between 4.3 mg. and 6.5 mg. per 100 ml., and the alkaline phosphatase between 1.9 and 3.6 units. The nonprotein nitrogen gradually rose to between 82 mg. and 106 mg. per 100 ml. The hemoglobin ranged between 8.3 gm. and 10 gm. per 100 ml. There were occasional episodes of confusion.

During one of these episodes on the sixty-fourth hospital day the patient sustained a subtrochanteric fracture of the left femur. Throughout the hospital course there was a gradual development of gangrene in the left foot. A high amputation of the left thigh was performed on the eighty-third hospital day, when, after three transfusions of blood, the hemoglobin was 8.3 gm. per 100 ml. The amputation specimen, in addition to gangrene, showed metastatic calcification of the soft tissues as well as marked arteriosclerosis and phlebosclerosis.

The postoperative course was complicated by episodes of vomiting and diarrhea with dehydration, serum electrolyte imbalance and an infection caused by *Staphylococcus aureus* at the operative site. An upper gastrointestinal series on the tenth postoperative day demonstrated marked deformity of the duodenal bulb and the previously noted small ulcer crater in the proximal portion of the duodenal bulb; there was slight dilatation of the proximal portion of the jejunum; no marginal ulcer was seen. The serum calcium ranged between 8.7 mg. and 9.6 mg., and the phosphorus between 3.5 mg. and 5.5 mg. per 100 ml. Despite fluids given intravenously and a feeding jejunostomy, the patient became disoriented and gradually became unresponsive. The nonprotein nitrogen ranged between 67 mg. and 112 mg. per 100 ml. He died on the thirty-fourth postoperative day. Terminally a pleuropericardial friction rub was audible.

Differential Diagnosis

Dr. Alexander Leaf*: In summary this middle-aged man had a long-standing history of peptic ulcer treated for many years with milk and antacids. Unfortunately, no estimate of quantities of milk and alkali ingested is given. Clinical evidence of renal impairment began about seven years before admission and was confirmed by laboratory studies at another hospital. The elevated nonprotein nitrogen, the normal serum calcium, the elevated serum phosphorus and the normal carbon dioxide found then are noteworthy. Subcutaneous swellings, largely periarticular in distribution, also developed at this time. In the subsequent years, symptoms of renal insufficiency and of peptic ulcer persisted; the latter was complicated by surgery in the form of a gastroenterostomy and by massive gastrointestinal hemorrhage. He continued to seek relief from the ulcer with milk and alkali therapy; though, again, the amounts are not given.

When admitted here he had renal failure, with hypercalcemia, hyperphosphatemia and subnormal calciuria. Is my conclusion about that calcium excretion correct? Only the concentration is given, without the twenty-four-hour urinary volume. Is that information available?

*Assistant physician, Massachusetts General Hospital.

Dr. Robert E. Scully: There are many determinations. The first twenty-four-hour specimen had a volume of 980 ml.; the calcium was 6.7 mg., and the phosphorus, 43 mg. per 100 ml.

Dr. Leaf: So there was a very low calcium excretion. The patient had peptic ulcer, extensive metastatic calcification without bone disease, arterial insufficiency of the lower extremities, necessitating amputation of the left leg for gangrene, and a downhill course postoperatively.

May we see the x-ray films? I am particularly interested in metastatic calcification of the bones and kidneys and the fracture sustained in the femur.

Dr. Jack Dreyfuss: From the many films on this patient I have arbitrarily selected a few covering a period of several months. The initial film shows the area of amorphous calcification adjacent to the olecranon of the right arm, either in the bursa or close to it (Fig. 1). Other films at that time demonstrate arteriosclerosis in vessels about the ankle and the wrist joint of a degree not usually seen in a patient of this age. Extensive calcification in the splenic and the left iliac arteries and an area of calcification in the left leaf of the diaphragm are also seen. There are other scattered areas of amorphous calcification about the shoulder and axillas; these are most striking about the hip joints. Where they can be seen through this calcification, the articular margins of the joints are intact, and the bone itself appears to be normal. In a film from a gastrointestinal series there is a suggestion of a marginal ulcer in the proximal part of the jejunum past the stoma. A film taken during an intravenous pyelogram demonstrates that the spleen is enlarged and that there is no contrast material in the drainage system on either side although there is some in the bladder.

Dr. Leaf: Are the kidneys small, and do they show any calcification?

Dr. Dreyfuss: The outlines are not distinct; they appear to be small. There is no suggestion of calcification in their substance.

Dr. Leaf: Do you have films of the left femur?

Dr. Dreyfuss: I think that it is only fair to say that there was some disagreement about whether or not this was a fresh fracture of the femur. Most of the radiologists believed that it was. In the films taken after the fracture was first described clinically there is distortion of the left hip. In the films taken before that time there was also a deformity on that side. Laminagraphic studies do not demonstrate a definite fracture, although there is again the gross deformity. Underneath this amorphous calcification there could be fracture lines. The remainder of the bones are normal.

Dr. Leaf: It seems to me that the differential diagnosis includes conditions in which both hypercalcemia and renal failure may be associated. These are acute osteoporosis, metastatic neoplasm with bone involvement, sarcoidosis, myelomatosis, vitamin D

intoxication, hyperparathyroidism and the milk-alkali syndrome. Simple renal failure, though it could account for much of the picture, cannot result in elevation of the serum calcium concentration above the normal level and will thus be discarded. The possibility that two independent diseases are responsible for the renal failure and disturbed calcium metabolism will also not be considered. The peptic ulcer was repeatedly demonstrated roentgenographically; it behaved like a peptic ulcer clinically, and I think we can all agree that it was a peptic ulcer, whatever its etiology.

I can rapidly reduce the list of possibilities to two conditions and then cannot go beyond this except by guesswork. Acute osteoporosis requires no further comment in view of the long history. Metastatic neoplasm is excluded by the long clinical course and the normal bones verified by both x-ray examination and biopsy. Sarcoidosis is excluded by the absence of discrete bone lesions, a normal serum protein pattern and the low urinary calcium excretion. The normal appearance of the bones in the x-ray films and the biopsy of bone marrow render multiple myeloma unlikely, as does the long clinical course. Vitamin D intoxication could account for the entire clinical picture, aside from the peptic ulcer. I am entirely at the mercy of the historian in discarding this diagnosis; no mention of vitamin D intake is present in the history, nor is there any complaint for which it is likely that this drug was self-administered.

This leaves two remaining possibilities of hyperparathyroidism complicated by renal failure and the milk-alkali syndrome. Long-standing symptoms of peptic ulcer treated by prolonged and excessive intake of milk and absorbable alkali are the *sine qua non* of the milk-alkali syndrome, but symptoms of the actual presence of peptic ulcer occur so commonly in association with primary hyperparathyroidism that this feature in the present case is hardly diagnostic. Furthermore, in the history an excessive ingestion of milk and alkali was not emphasized; so that we could be dealing with a case of hyperparathyroidism with a coincidental peptic ulcer, the treatment of which either played no part in the renal disease or only aggravated the renal lesion of hyperparathyroidism.

Hypercalcemia, of course, is associated with both hyperparathyroidism and the milk-alkali syndrome. Whereas a low serum phosphorus concentration is the usual finding in hyperparathyroidism and a high value is expected in the milk-alkali syndrome, the serum phosphorus concentration may become elevated in hyperparathyroidism if renal failure ensues. Hence, the serum concentrations of both calcium and phosphorus do not help to distinguish between these two possibilities.

The urinary calcium excretion may be expected to be increased in hyperparathyroidism but not in the milk-alkali syndrome. With progressive renal failure, however, the rate of calcium excretion decreases even in hyperparathyroidism. Thus, in the famous case of Captain Martell studied extensively by Albright and his associates[1] the urinary calcium excretion was 1.31 gm. per twenty-four hours in 1926 before renal impairment, and on the same intake dropped to 0.27 gm. per twenty-four hours in 1933 after renal impairment had developed (nonprotein nitrogen, 58 mg. per 100 ml.). On the same diet, however, the control subjects excreted an average of 0.130 gm. per twenty-four hours. The low rates of calcium excretion, which I calculated to be about 60 mg. per twenty-four hours in the case under discussion, could have resulted from the presence of more advanced renal failure than in other cases with either condition that have been studied so far.

The normal serum alkaline phosphatase and absence of bone disease in the x-ray films and biopsy are, of course, expected in the milk-alkali syndrome but also are the findings in a patient with primary hyperparathyroidism who has a high calcium intake, as this patient apparently did.

Metastatic calcification is common to both conditions, and the ocular calcification in the patient under discussion has been described repeatedly in both conditions. Whereas calcification of kidneys, stomach and lungs is also common in hyperparathyroidism, such extensive soft-tissue calcification, especially the large subcutaneous deposits, certainly must be unusual in hyperparathyroidism. In fact it is hypoparathyroidism, rather than hyperparathyroidism, that is likely to be associated with extensive subcutaneous calcification. This finding I thus take to support the milk-alkali syndrome; I found 1 such case in the literature with subcutaneous calcification apparently as extensive as this patient had.[2]

There are two criteria by means of which a nearly absolute distinction between hyperparathyroidism with advanced renal failure and the milk-alkali syndrome might have been made, but unfortunately the clinical record fails us on both these counts. The first of these is the presence of at least mild alkalosis as manifested by an elevated serum carbon dioxide content in the presence of the elevated nonprotein nitrogen in the milk-alkali syndrome. As you all know, acidosis is the expected finding in uremia, even when the uremia is complicated by considerable vomiting. The presence of even a mild alkalosis would, therefore, have been strong evidence in favor of the ingestion of excessive quantities of absorbable alkali. The only serum carbon dioxide content reported was a normal value obtained at another hospital seven years before admission here. Even a normal carbon dioxide in the presence of a nonprotein nitrogen of 130 mg. per 100 ml. is suggestive of the milk-alkali syndrome, but it would be more helpful to know what this value was when the patient first entered this hospital.

DR. SCULLY: The carbon dioxide content was 27 milliequiv. per liter.

DR. LEAF: That value is normal, and I should expect some degree of acidosis with the degree of uremia present.

The final possible distinguishing point is the clinical improvement and decrease in serum calcium and phosphorus values to be expected in the milk-alkali syndrome upon withdrawal of the excessive amounts of calcium and absorbable alkali. In hyperparathyroidism, though the serum calcium concentration is somewhat influenced by the calcium intake, it would not be expected to return to normal concentrations on a low-calcium diet. Unfortunately, the patient died before any such clinical trial could be attempted.

Although I have stated that an absolute differential diagnosis between hyperparathyroidism complicated by renal failure and the milk-alkali syndrome cannot always be made clinically, I shall cast my vote in favor of the milk-alkali syndrome in this case. I anticipate that no parathyroid tumor was found at autopsy, but that extensive and widespread soft-tissue calcification was present, with marked vascular calcification and insufficiency. The kidneys probably showed, in addition to metastatic calcification, evidence of pyelonephritis. Evidence of more widespread infection was likely in view of the terminal wound infection with *Staph. aureus.*

DR. REED HARWOOD: Is the alkali an essential ingredient in producing the syndrome?

DR. LEAF: It is difficult to distinguish which is to blame, — the calcium or the alkalosis, — but apparently the full-blown syndrome does not occur without a high-calcium and a high-alkali intake. The high-calcium intake damages the kidneys, producing nephrocalcinosis, or stone formation.

A PHYSICIAN: Eight years before admission, when the patient was operated on for intestinal obstruction, the surgeon noted that the kidneys were small. X-ray films of the chest and abdomen at that time gave no evidence of metastatic calcification.

DR. LEAF: The full-blown syndrome of metastatic calcification after excessive milk and alkali ingestion has been described in patients with an underlying primary renal disease, such as pyelonephritis or glomerulonephritis. In such patients the signs of the milk-alkali syndrome would probably develop with perhaps even a lower intake of absorbable alkali and calcium than in those without underlying renal disease. I suspect that some evidence of primary renal disease was found.

A PHYSICIAN: What features are against a collagen disease?

DR. LEAF: In the collagen diseases in which peripheral calcification occurs there are a few distinctions: the serum calcium and phosphorus are not elevated. There, the calcifications seem to be secondary to damage of tissue, whereas, in this case, I think that the calcification was the primary event as a result of supersaturation of the body fluids with the calcium and phosphorus. Furthermore, in some of the collagen diseases there is bone being laid down, rather than amorphous masses of calcium as here.

DR. FLETCHER S. COLBY: Does one not usually find renal stones in these cases?

DR. LEAF: They have been described in this syndrome. I think there was a fair amount of calcification within the kidneys microscopically, even if this does not show in the x-ray films. The failure of the kidney to concentrate the urine after nephrocalcinosis develops seems in some cases to be a preventive against stone formation; so that one or the other may be present.

DR. BENJAMIN CASTLEMAN: Is it ever possible to have a high serum calcium in a case of secondary hyperparathyroidism that results from chronic renal disease?

DR. LEAF: As I understand it, with renal failure and phosphate retention there is a reciprocal drop in the serum calcium, and secondary hyperparathyroidism develops; that hyperparathyroidism is secondary, however, only in that it is — speaking teleologically — an attempt to correct the blood levels. It seems unlikely, therefore, theoretically that it would actually produce supranormal blood levels. In my experience I do not recall having seen a case of primary renal failure at a terminal stage in which there was an elevated serum calcium level.

DR. JACOB LERMAN: Have you ever seen a calcium of 14 mg. per 100 ml. in a patient with the milk-alkali syndrome?

DR. LEAF: I have not, but it has been described.[3]

DR. LERMAN: And verified at post-mortem examination?

DR. LEAF: Yes.[3]

DR. SCULLY: Dr. William H. Baker, who did studies with radioactive calcium on the patient, is not here. However, Dr. Sohier can discuss the results.

DR. WILLIAM D. SOHIER, JR.: I saw the patient only on one or two occasions. I can give the results of the radioactive studies. Twenty-four hours after ingestion of radioactive calcium there was only 2 per cent remaining in the blood. That is a rapid fall: the normal level is between 10 and 12 per cent. Four hours after the ingestion of radioactive calcium, a biopsy of an area of metastatic calcification revealed some cheesy material that exhibited radioactivity in significant amounts. In other words the turnover in the metastatic areas was rapid.

DR. PHILIP H. HENNEMAN: Attempts were made to obtain a history of vitamin D ingestion from the patient and his family. These were unsuccessful except for a history of ingestion of Zymacaps, of which he never took an excessive number. The diagnosis we made was also milk-alkali syndrome. In the last few years we have seen several cases presenting the general picture of the milk-alkali syndrome without systemic alkalosis. Indeed, in the original report it was noted that when the patients stopped taking alkali they often continued to have hypercalcemia

for many months but that the alkalosis often disappeared promptly. It may be that the alkalosis is not an essential part of this syndrome. We believe that this diagnosis cannot be made with certainty until primary hyperparathyroidism has been excluded by cervical exploration. The suggested causes of the syndrome have never been entirely convincing, even to Dr. Albright, one of the authors[4] who described the syndrome originally. One reason for this is that only a very small percentage of patients ingesting large quantities of milk acquire hypercalcemia. Currently, attention is focused on a number of conditions in which hypercalcemia results from markedly increased calcium absorption; these include sarcoidosis, idiopathic hypercalcemia in infancy, primary hyperparathyroidism and, of course, excessive vitamin D ingestion. This man was studied to ascertain if he had an increased calcium absorption or a hypersensitivity to vitamin D.

The significance of the radioactive calcium studies seems to be that the large masses of metastatic calcium are readily exchangeable with the blood calcium. It may be that even after the high calcium intake has stopped, those areas may easily feed back calcium to the serum and thus maintain the hypercalcemia.

Incidentally, the diagnosis of fracture of the femur seemed certain from the clinical findings. On reviewing the films taken before the fracture, Dr. William H. Baker and I could not see the bony cortex in the region of the eventual fracture, and we were concerned that this area might represent metastatic carcinoma from a silent primary lesion.

DR. LEAF: Regarding Dr. Henneman's comment, I think that when one looks back at the old Sippy regimen for peptic ulcer, in which 4 or 5 gm. of calcium carbonate or magnesium carbonate was alternated at hourly intervals with a similar amount of sodium bicarbonate, it is surprising that every patient did not present this syndrome. That may be evidence that the absorption of calcium differs radically in patients or that the tendency to precipitate in the tissues differs. About the changeability of deposits, there has been a case reported in which cessation of the high-calcium and high-alkali intake not only produced a gradual fall in the blood level but also caused the huge masses of metastatic calcification to disappear.[2]

DR. SCULLY: Dr. Shaw, will you comment on the relation of hypercalcemia and peripheral vascular disease in this patient?

DR. ROBERT R. SHAW: The mechanisms of formation of arteriosclerosis are not well understood. We do know, however, that calcification may occur in any degenerating avascular tissue. I suspect that this patient's arteries were so apparent in the films because he had much more calcium in the degenerated areas than the ordinary person has, and I should not blame the arterial insufficiency on the calcium deposition particularly.

Arterial calcification appears in the media in medial arteriosclerosis and in the subintimal plaques of atherosclerosis. The former may show a delicate three-dimensional tracery of vascular anatomy in the x-ray films, but is not necessarily correlated with arterial insufficiency and arterial occlusive disease. The calcification of atherosclerosis appears on the x-ray films as isolated chunks of calcium, rather than outlining the complete structure of the vessel. This type of calcification, of course, is correlated with arterial occlusive disease.

CLINICAL DIAGNOSIS

Milk-alkali syndrome.

DR. ALEXANDER LEAF'S DIAGNOSES

Milk-alkali syndrome.
Nephrocalcinosis.
Pyelonephritis.

ANATOMICAL DIAGNOSES

(Milk-alkali syndrome), with metastatic calcification of soft tissues, kidneys, pulmonary vessels and dura mater.
Chronic pyelonephritis.
Duodenal and stomal ulcers, active.
Atherosclerosis, with thrombosis of left external iliac artery.
Bronchopneumonia.
Fracture of left femur.
Splenomegaly.

PATHOLOGICAL DISCUSSION

DR. SCULLY: At autopsy the organs of greatest interest were the kidneys and the parathyroid glands. The kidneys were small, weighing 60 gm. each. Their external surfaces were coarsely granular. On section whitish-yellow, chalky streaks were visible in the pyramids. Microscopically, these streaks proved to be masses of calcium, both within the tubules and in the interstitial tissue between the tubules. Throughout the renal cortex there were numerous large areas characterized by deposition of calcium casts within tubules, sclerosis of glomeruli, tubular atrophy, chronic inflammatory-cell infiltration and interstitial fibrosis (Fig. 4). We interpreted these renal findings as nephrocalcinosis, complicated by chronic pyelonephritis and nephrosclerosis.

The parathyroid glands were not grossly enlarged. Microscopically, however, they showed secondary hyperplasia. Most of the gland tissue was composed of broad cords of chief cells with little fat between them. There were a few solid, adenomalike nodules of microscopic dimensions, composed of chief cells (Fig. 5). Another nodule, 3 mm. in diameter, was made up entirely of oxyphil cells, which are thought to be involuted, nonfunctioning parathyroid cells.

Such nodules as these are probably not true tumors and may be seen in secondary hyperplasia. There

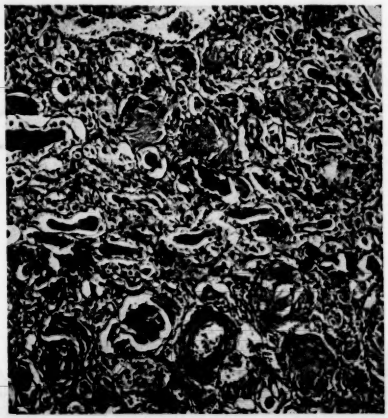

FIGURE 4. *Kidney, Showing Calcium Casts in Tubules (Black), Sclerotic Glomeruli (Large, Round Hyaline Masses) and Atrophic Tubules.*

was nothing to suggest primary hyperfunction of the parathyroid glands. The bone in general looked nor-

FIGURE 5. *Parathyroid Gland, Showing Hyperplasia of Chief Cells, with Reduction of Fat (Lower Portion of Picture) and Solid Nodule Composed of Smaller Chief Cells (Upper Portion of Picture).*

mal; there was no osteoporosis or osteitis fibrosa cystica, in spite of the well marked parathyroid hyperplasia. Osteitis fibrosa cystica does not always accompany hyperparathyroidism, but when the hyperparathyroidism, even if secondary, has this long a duration, one reasonably expects some evidence of bone resorption unless some complicating factor exists. Here, of course, the high intake of calcium probably prevented the development of bone disease.

The left femur did show a fracture pathologically. Microscopical sections in the region of the fracture

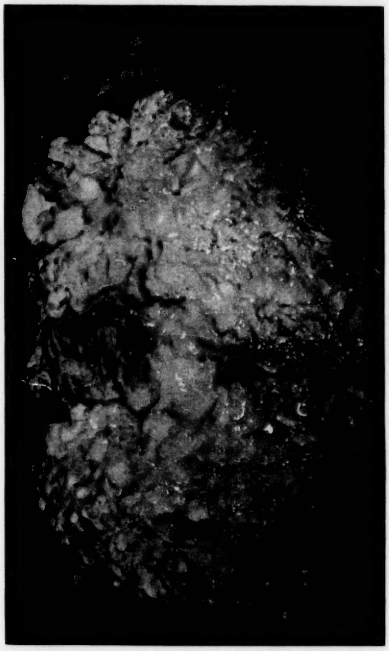

FIGURE 6. *Sectioned Surface of the Chalky Mass in the Axilla.*

disclosed osteoporosis, which, I suppose, may have been due to a combination of vascular insufficiency and disuse, for this was the only site at which the bone was thinner than normal. The large soft-tissue masses were composed of white, gritty, chalky material (Fig. 6). Microscopically, this appeared as amorphous débris surrounded by foreign-body giant cells. Minor amounts of calcium were deposited in the dura mater and diaphragm and the walls of several small pulmonary veins.

There was a duodenal ulcer as well as an ulcer of the jejunum near the stoma of the gastrojejunostomy. Both were active. To explain the gangrene of the left lower extremity we found a thrombus completely occluding the left external iliac artery,

which, together with the aorta, showed severe atherosclerosis. I might mention that in the arteries of the left leg most of the calcification was in the media, and was therefore unrelated to the atherosclerotic process causing the patient's vascular insufficiency. The spleen was quite large, weighing 750 gm. Microscopically, it showed only severe congestion of the red pulp. Possibly, its enlargement was related

FIGURE 7. *Biopsy Specimen of a Normal Kidney (Case 3 of Burnett et Al.*[4]*).*

to chronic pyelonephritis, which often seems to be accompanied by splenomegaly. The liver appeared normal. The lungs showed foci of bronchopneumonia.

As we reconstruct the case, then, the patient suffered progressive renal impairment while on a high-calcium and high-alkali intake. Parathyroid hyperplasia was a secondary phenomenon. One of the problems concerning the milk-alkali syndrome is whether or not it can develop in the absence of preexisting renal disease. The present case is not helpful in this regard. However, in reviewing our autopsies of this disease we encountered a pertinent case of a patient who was Case No. 3 in the original report of Burnett et al.[4] and who was still alive at that time. This patient, who had been taking milk and antacids off and on for twenty-five years for an ulcer, had a left-sided lumbar sympathectomy for intermittent claudication in 1941. At this time he had a perfectly normal-looking kidney on biopsy (Fig. 7). A year and a half later at another hospital, the nonprotein nitrogen was reported as 198 mg. per 100 ml. He improved considerably after intravenous therapy. Five years postoperatively he showed the fully developed milk-alkali syndrome; the nonprotein nitrogen was now 95 mg. per 100 ml. On a low-calcium diet there was clinical improvement and return of blood chemical levels toward normal. He died of uremia and pulmonary edema eight years after the renal biopsy. The process that precipitated his death was thrombosis of the aorta and left renal artery, with extensive infarction of the left kidney. In addition to the infarction, the kidneys showed moderate nephrocalcinosis and a considerable, but patchy, chronic pyelonephritis (Fig. 8). Again, there was secondary hyperplasia of the parathyroid glands. Although by no means conclusive, the chronology and findings of this case suggest that the milk-alkali

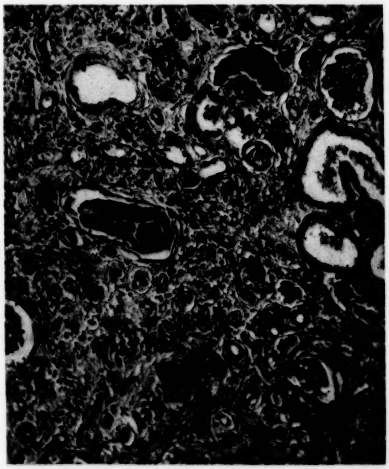

FIGURE 8. *Autopsy Specimen of the Kidney (Case 3 of Burnett et Al.*[4]*).*

Note the crescent-shaped calcium cast in the tubule and chronic inflammation and fibrosis of interstitial tissue.

syndrome with reversible renal impairment can occur before the development of organic renal disease.

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EXTRASENSORY PERCEPTION

TELEPATHY, foreknowledge, clairvoyance, spiritualism in the sense of communication with that well known, unknown bourne from which no traveler, it is said, returns, and the influence of the happy medium have challenged the human intelligence for centuries. Their reception has varied from a general acceptance in uncritical times and places to indifference, skepticism, denial or hostility in a period that is dominated by science and characterized by a devotion to the physically demonstrable.

And still certain facts and credible observations remain, sufficiently clear and of such authenticity as to invite the serious consideration of philosopher and scientist alike. To bring some of these persons together in an attempt at the organization and presentation of the material on psychical research, the Ciba Foundation of London, credited in this instance with what was called "incredible courage," arranged an international symposium on the subject. The papers and their discussion have been published by J. & A. Churchill Ltd., of London, and Little, Brown and Company, of Boston, under the title *Extrasensory Perception*.

Extrasensory perception is defined in the *Journal of Parapsychology* as the "response to an external event not presented to any known sense." Unrelated by definition to instinct, which is an "involuntary or unreasoning prompting to any action," it may have reference to a sixth sense as yet unidentified; but in that case it is automatically removed from the extrasensory category. For man can accept with complacence any demonstrable cause and effect, however complicated, from the unfolding of a seed to the communication system of ants and bees, but views with skepticism the mystic art of water dowsing, forgetting that his aboriginal prototype is apparently able to detect the presence of water on his approach to a hidden source, even without the divine agency of a forked stick.

Despite the serious attention that has been turned to it for years "the field of extrasensory research remains a no man's land between the lunatic fringe on the one hand and the academically unorthodox on the other." For modern times "serious attention" may be dated from 1882, in which year the Society for Psychical Research was founded. An obstacle to scientific achievement in such a field rests in the lack of any unity of opinion regarding what constitutes valid evidence.

Indifference or hostility to psychical research, according to J. Fraser Nicol, of Cambridge (Massachusetts), is based on four factors. These he lists as the apparent irrelevance of psychical research to other scientific fields, the failure of psychical researchers to obtain *reproducible* phenomena, discordant views on the validity of evidence and inflated claims to discoveries. The only actual statistical evidence in

favor of extrasensory perception is based on experimental demonstrations of card calling, sight unseen, representing factual observations that cannot validly be disbelieved. Such evidence, on the other hand, based on the performance of certain persons in whose mental life extrasensory perception is an unpredictable phase and not a permanent quality, is "suggestive but not conclusive." It gives to the results an appearance of respectability lacking in the amorphous mass of experiential evidence that has been accumulated. The difficulty of separating table tipping and other uncontrolled forms of parlor entertainment from serious experimentation and observation remains.

An opinion that expresses admirably the mind open to a belief in extrasensory perception was Freud's decision to revise his fear that this belief might endanger the scientific outlook; such a fear, as he phrased it, "displays no great trust in science."

A distressing tendency of some of the participants in a discussion of this nature is to resort to technical jargon, thus sharply limiting the size of the understanding and possibly sympathetic audience. As so often happens, mere man becomes charmed with the sound of his own syllables and inordinately pleased with his ability to speak in a tongue beyond the comprehension of merer mortals.

When the advances of physical science and the magic of modern communication are taken into consideration the boundaries between sensory and extrasensory seem less definable. For there are more things in heaven and earth than were dreamt of, even in Horatio's philosophy.

CHANGE IN COMMITMENT LAWS

One of the weaknesses under the Massachusetts law in the temporary-care commitment of patients for evaluation of mental status has been the difficulty of holding them in the hospital on a temporary-care paper as long as may be needed. Since temporary-care commitments have been limited to ten-day periods it has always been necessary to apply to the court for a further commitment for an indefinite time, in order to complete the desired investigation. Such an application requires a notice to the patient of his right to a hearing, with two days in which he may make the request and with an allowance of several days for the court to hold the hearing.

The state hospitals and the McLean Hospital in Waverley have had an observation commitment to fall back on, but the private hospitals have not been permitted by law to accept observation cases. The original acts were obviously designed to protect the rights of individuals and to secure them against unnecessary curtailment of liberty, but in practice their best interests and those of the community have suffered as a result of these generally praiseworthy precautions.

Effective on this date, therefore, the laws pertaining to commitments to the mental hospitals of the State have been changed by the enactment of Chapter 589 of the *Acts* of 1956. The new law, sponsored by the Department of Mental Health, changes Section 79 of Chapter 123 of the *General Laws* to permit an extension of the ten-day temporary-care period if application for prolonged judicial commitment should be found necessary. The patient, if this extension is deemed desirable, may now be detained on a temporary-care paper until the court has acted on the prolonged-commitment application, provided it has been made prior to the expiration of the ten-day initial period.

In compliance with this change in the law, the Department of Mental Health form known as "D.M.H. Form 5" has been modified to become "D.M.H. Form 5, Revised 1956." This change becomes effective on November 1, 1956, after which date the new forms will be used. These may be obtained from the state hospital or school nearest the physician's office, the district court serving the town or the Department of Mental Health, 15 Ashburton Place, Boston.

RED FEATHER CAMPAIGN

In accordance with a custom now almost immemorial to its younger representatives, the denizenry of Greater Boston, so-called, has embarked upon its annual Red Feather Campaign. This solicitation, as is well known, is for the support of those many indispensable social and charitable agencies of the area that must maintain their essential services independent of the spectacular national drives with their capacity for stirring men's souls to the bottoms of their pocketbooks.

The United Red Feather Campaign, which is being held this year from October 21 to November 20, has on occasion gone over the top, as it did in the prosperous year of 1955. Occasionally, it has failed to meet its goal, thus penalizing in some degree each of the vital charities that are dependent on it.

In the poetically prophetic words of the Campaign laureate, fortunately left nameless:

> Some folks vote for Ike,
> Some folks vote for Adlai,
> All folks vote for us
> For we serve all so gladly.

Thus inspired the medical profession may be expected to do its share in putting the campaign over, conscious of the fact that a campaign, like a soft drink, can fizzle out or go over the top, depending on the vigor with which it is shaken.

1957 PRIZE-ESSAY COMPETITION

The editors are pleased to announce that the ninth in the *Journal's* series of student prize-essay competitions is now open and will close on March 15, 1957,

on which date all manuscripts to be submitted must be in their hands.

The nature of the competition has been such that it fits readily into the curriculum of the fourth-year student, requiring little extra work other than the preparation of the manuscript. This plan will be followed again, and the essay will consist of the report of a clinical case personally investigated by the student in the course of his or her academic work, combined with a discussion of the pathologic condition represented by the case and a review of the important literature on the subject. It should follow the usual form of case reports as published in the *Journal*.

The number of essays submitted and the gratification and appreciation usually expressed by the prize winners on being notified of their success make this one of the *Journal's* particularly pleasant enterprises.

The usual terms of the competition will apply:

Manuscripts must be not more than 5000 words in length, clearly typewritten in English, double or triple spaced, with references listed at the end in numerical arrangement according to the form used by the *Quarterly Cumulative Index Medicus*. They must be accompanied by a certification from the dean of the medical school concerned stating that the author is a member in good standing of the fourth-year class and specifying the expected date of graduation. No manuscripts will be returned.

A cash prize of $150 will be paid for the best essay of those found to be suitable for consideration, and the paper will be published in the *Journal* if the quality is considered to conform to the standards by which the editors usually judge material submitted; the author will receive a hundred free reprints. A second prize will consist of $50, and a third prize of a two-year subscription to the *Journal*. The editors reserve the right to withhold the awarding of any prizes if no papers of sufficient merit are submitted.

It is emphasized that in establishing this competition the editors are interested as much in encouraging good medical writing as in promoting the collection of scientific and clinical material. Particular attention will accordingly be paid to clarity, simplicity and general literary excellence.

"If the accoucheur would bear in mind, and act with a female as he would wish another accoucheur to act with his own wife, he cannot be far wrong." R.H.S.

Boston M. & S. J. *November 6, 1856*

MASSACHUSETTS MEDICAL SOCIETY

COMMITTEE ON MATERNAL WELFARE

Rupture of the Uterus

A thirty-eight-year-old gravida 5, para 4, died after a cesarean section at thirty-four weeks.

Of her 4 children only 2 survived early childhood, 1 having been stillborn at term and another having died at the age of eight months. The original cesarean section was necessitated by premature separation of the placenta at thirty-four weeks. The patient had almost died during this experience and had been given fourteen transfusions. She was advised not to get pregnant again and later refused a hysterectomy.

Until the day of admission the present prenatal course was uneventful except for a hemoglobin of 68 per cent (Sahli). At thirty-four weeks, she reported a sudden, extremely severe, sharp abdominal pain at 8:00 a.m. She was admitted to the hospital at 9:30 a.m. with a rapid pulse and appearing extremely apprehensive. The uterus was described as hard, and she was thought to be in irregular labor; the cervix was not dilated. The fetal heart sound was not heard. Given mild narcotic sedation during the day for her pain, she was merely observed, and that evening a transfusion of 400 ml. of whole blood was given because of the anemia. On the following morning at 3 o'clock pains became much worse but were described as "labor not progressing normally." She received 2 more transfusions without improvement either in hemoglobin or in general condition. At about 4:00 p.m. — that is, thirty hours after admission — consultations were requested. An obstetrician described the uterus as tetanically contracted, the abdomen as hard and boardlike and the patient as in shock; he made a diagnosis of abruptio placentae, and recommended immediate cesarean section. An internist stated, "I do not believe the basic difficulty is cardiac but rather overwhelming infection, perhaps renal — the high white-cell count may be a good omen."

Accordingly, after antibiotics and further transfusions, a cesarean section was undertaken, with a pulse of 128, respirations of 40 and a blood pressure of 98 systolic, 60 diastolic. The induction of anesthesia with thiopental sodium and nitrous oxide and oxygen was very stormy. Gastric fluid was obviously regurgitated, but bronchoscopy was performed immediately, foreign material being removed from the bronchial tree, where free blood was also seen. Despite severe bronchospasm, anesthesia was started again, and laparotomy was finally performed. At operation the abdominal cavity contained a large amount of old and new blood as well as the fetus and placenta, which had escaped through a rupture in the scar from the previous cesarean section. Although the uterus was repaired and the abdomen closed as rapidly as possible, the patient's condition remained critical, and the postoperative course was marked by noisy breathing, pulmonary congestion and a rapidly rising pulse and temperature. She died at 9 o'clock on the following morning, forty-eight hours after admission and approximately fifteen hours postoperatively.

Like many deaths due to rupture of the uterus this was classified as preventable. Since the patient had had a stormy time with one previous pregnancy and had been advised not to undertake another pregnancy — in fact she had refused hysterectomy — the responsibility for this must lie in no small way upon herself.

It seems apparent with the advantage of hindsight that the uterus ruptured at home just before admission. This diagnosis must not have been evident at the time although strongly suggestive signs were described in the record. These were not neglected, but it might be said that consultations were requested much too late since apparently too much was attributed to the pre-existing anemia. Abdominal pain, "irregular labor" and lack of progress in the presence of a scarred uterus hardly result from a low hemoglobin level and should have prompted a call for help in less than thirty hours. This is probably the severest criticism that is justified since the subsequent downhill course was largely due to this delay. Whether the same difficulties of anesthesia would have arisen if operation had been done on admission is conjectural, but the patient's ability to cope with them would certainly have been better. Death, ultimately assigned to rupture of the uterus, may actually have resulted from the immediate effects of aspiration pneumonitis.

It has been said that immediate bronchoscopy almost always prevents death from aspiration and that deaths result from failure to recognize this accident. Since an alert anesthetist not only recognized it here but also applied the proper treatment instantly, this case must represent one of the exceptions and is of course explained by the patient's poor condition.

This case illustrates several features often seen in maternal death: first and foremost, the often-deprecated but terrifying inherent hazard of repeat cesarean section; secondly, the added threat of secondary anemia when hemorrhage is superimposed; thirdly, the deadly effect of delay; fourthly, the enormous responsibility incumbent upon anesthetists in complicated obstetric surgery; and, finally, the fact that reasonably healthy mothers can tolerate one or sometimes two serious complicating factors, but will often succumb when yet another burden is added.

JOHN FIGGIS JEWETT, M.D.
Chairman

CORRESPONDENCE

MEANS VERSUS ENDS

To the Editor: Reading the editorial, "The Play of the Market Place," in the September 13 issue of the *Journal*, I recalled reading in *Mental Hygiene* (15:34-44, 1931) a paper entitled "Personality: A study in the history of verbal meanings" by Thomas J. McCormack, LL.D., Superintendent, La Salle-Peru Township High School, La Salle, Illinois, who brings out that "the world is . . . viewed . . . under the aspect of the bargain-sale counter [and] salesmanship is the supreme objective of life." His article continues as follows:

> Several years ago, the president of the Inter-State University of Oklahoma asked an oil magnate of that commonwealth to endow a chair of Mid-Victorian Romanticism. The magnate declined the honor, but countered gallantly with a proposition to endow even more richly a chair to be known as the Chair of Personal Relations. He wrote a letter to the president in which he declared success in life to be the outcome of facility in personal relations — or of that ease and grace of human intercourse which give "efficiency to business and social life" and "lubricate" their activities. As with Goethe, so with this gentleman, personality was the key to a fully realized and completed human life.
>
> The idea is a commendable one and gives academic reality to a movement of thought that bids fair to humanize education. But back of the idea there lurks an ethical fallacy that must be scotched. It is the common fallacy of confounding means and ends, of substituting instrumental values for final and intrinsic values, of making wealth and material things the goal of life instead of using them as the means of attaining that goal. It is the characteristic fallacy of contemporary civilization. The only kind of human being known to the majority of successful men today in nearly all countries is the "economic man", the efficient producer, but more especially the perfect consumer. All the resources of arts, science, psychology, literature, and ethics are conscripted in the service of this dominant aim of our present-day civilization — to increase our wealth by sales to our meek and unsuspecting, our *de*-personalized fellow creatures. In this philosophy man is not an ethical animal, a *person*. Man is *par excellence* a customer. The world is not viewed as Spinoza viewed it under the aspect of eternity, but under the aspect of the bargain-sale counter. Salesmanship is the supreme objective of life, and personality is conceived as the delicate precision instrument by which its ends are effected. And so is being written on acres of Canadian pulp the last decadent chapter in the history of a royal concept which began its life some twenty-four or twenty-five hundred years ago and which has played a part in nearly every department of human thought — in the drama, in jurisprudence, in philosophy, in literature, in psychology, and in the science of the nature of God.

EMANUEL ANASTASSOFF, M.A.
Milton, Massachusetts

REGARDING DIFFUSIBILITY OF SULFONAMIDES

To the Editor: The article "Current Concepts in Therapy: Sulfonamides" appearing in the August 9 issue of the *Journal* attracted my attention by reason of its contents but more specifically because of the intriguing footnote, "Prepared under the supervision of the *Journal's* Committee on Advertising." This seems to imply that the *Journal* has undertaken the praiseworthy but difficult task of refereeing to some extent the advertising material in its pages and of supplying at the same time to its readers the broadly accepted facts that will enable anyone better to judge claims wherever they are found. It seems obvious that with the reputation and authority of the *Journal* behind such pronouncements, the opinions of the Committee on Advertising will be looked upon as prime, quotable material.

It is for that reason that this letter is written to inquire whether at least one statement in this article does not need some clarification or modification: "After absorption the sulfonamides readily diffuse into all the body fluids, including the cerebrospinal fluid, where levels of 50 per cent or more of the blood level are easily attained." As it stands, this statement goes farther than the manufacturers of some of the sulfonamides have cared to go regarding their own products. It seems like a slight reversal in form for an impartial group to suggest broader claims than are presently being made by interested parties.

Accordingly, I am inclined to question whther the statement should be allowed to stand as it reads. First of all, there seems to be some need for qualification of "the sulfonamides," for certainly all the systemically employed sulfonamides do not behave uniformly regarding absorption, diffusion or tissue distribution. Specific sulfonamides do not diffuse into the cerebrospinal fluid to the extent indicated.

Secondly, it seems desirable that the statement give indication of cerebrospinal-fluid diffusion as it relates to the presence or absence of inflammation of the meninges. Diffusion does occur in greater degree in the presence of meningitis and in amounts approaching the figures cited, "50 per cent or more of the blood level," but even in this circumstance diffusion is not uniform and some published figures are lower than the level mentioned here. Hence, without qualification of inflammation of the meninges, it is my opinion that the Committee's statement is too liberal.

Thirdly, by "easily attained," I get the impression of *promptness* of attainment of the concentrations mentioned. If this assumption of meaning is correct, again the statement is more generous than can be supported by published work. Especially in the treatment of meningitis is the rapid attainment of effective concentrations important, and "easily" or "rapidly" in our hands has the connotation of the first hour or two after medication. Concentrations of "the sulfonamides" of "50 per cent or more of the blood level" are not "easily attained" in our hands.

These are meant to be constructive observations, and it is really in the spirit of applause and approval for the undertaking of the *Journal's* Committee on Advertising that this letter is written. It is clear that almost as soon as "impartiality" is claimed, it is doubted, and a few cries of anguish can be anticipated, some of them justified. For example, the laudable surgical skill that reduced the "over 5000" sulfonamides to a handful of useful drugs carried over and snipped a legitimate "e" from the generic name sulfisoxazole. And I daresay some of our foreign colleagues might demur on the deletion of sulfaguanidine from the list of useful, poorly absorbed sulfonamides. However, I anticipate that by far the majority of physicians and responsible scientists and physicians within the pharmaceutical industry itself will applaud the efforts of the Committee on Advertising. The onus that it has taken upon its shoulders is a heavy one, and a vigorous reader reaction can be anticipated. I hope there will be a reasonable machinery for dealing with letters that do not stoop to idle carping.

In closing, three cheers for the *Journal* and the continuation of its many services in the cultural and intellectual areas!

WILLIAM P. BOGER, M.D.
Wayne, Pennsylvania

NONCLINICAL NOTES

BOSTON DISPENSARY

Dr. Hans Waine, of West Newton, Massachusetts, has been appointed chief of staff of the Boston Dispensary, a unit of the New England Medical Center. Dr. Waine, well known for his long service with the New England Chapter of the Arthritis and Rheumatism Foundation, received his degree from Harvard Medical School in 1937. Abbie E. Dunks, formerly director of the Dispensary, has been appointed to the newly created post of administrator.

NOTICES

BOSTON CITY HOSPITAL HOUSE OFFICERS' ASSOCIATION

The House Officers' Association of the Boston City Hospital announces the schedule of the Tuesday evening lecture series to be held in the New Cheever Amphitheater, Dowling Building, Boston City Hospital, at 7 p.m. There will also be a lecture held the last Thursday in November, in addition to the regular Tuesday lecture. The program is as follows:

November 6. Studies in Wound Healing, with Particular Reference to Humoral Factors. J. Englebert Dunphy, M.D., professor of surgery, Harvard Medical School, and director, Sears Surgical Laboratory and Fifth Surgical Service, Boston City Hospital.

November 13. Certain Aspects of Carbohydrate Metabolism and Diabetes. De Witt Stetten, Jr., M.D., associate director in charge of research, National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Maryland.

November 20. The Place of Cortisone in the Management of Arthritis. Joseph Lee Hollander, M.D., associate professor of medicine, University of Pennsylvania School of Medicine.

November 27. Severe Aortic Insufficiency: Unusual clinical features and criteria for selection for operation. W. Proctor Harvey, M.D., assistant professor of medicine and director of the heart station, Georgetown University Medical Center.

November 29. (Thursday). Experimental and Surgical Aspects of the Peptic-Ulcer Problem. Owen H. Wangensteen, M.D., professor of surgery, University of Minnesota Medical School.

December 4. The Relation of Endometrial Hyperplasia to Endometrial Adenocarcinoma. Edmund R. Novack, M.D., instructor in gynecology, Johns Hopkins University School of Medicine.

December 18. Cicatrizing Enteritis. Shields Warren, M.D., professor of pathology, Harvard Medical School, and pathologist, New England Deaconess Hospital.

AMERICAN CANCER SOCIETY GRANTS IN CANCER RESEARCH

The American Cancer Society is accepting applications for grants-in-aid for cancer research in the United States. Investigators now receiving support will hear directly from the Society concerning application for renewal grants.

Applications received before January 1 will be acted upon during the late winter and early spring and grants recommended will become effective July 1, 1957.

Further information may be obtained from the American Cancer Society, 521 West 57th Street, New York 19, New York.

WILLIAM OSLER MEDAL

To stimulate interest and research in medical history among medical students in the United States and Canada, the American Association of the History of Medicine has established the William Osler Medal, to be granted annually to the author of the best student essay submitted. All essays must be received before March 1, 1957, and should not exceed 10,000 words in length. The Association will consider unpublished essays by men and women who were students in schools of medicine and had not yet obtained their doctor's degree at the time that the essay was written, but it must be submitted before, or within, one year after the author's graduation. Preference will be given to essays that are the result of original research, but essays showing an unusual appreciation and understanding of historical problems will also be considered.

Further information may be obtained from Dorothy M. Schullian, Ph.D., Chairman, National Library of Medicine, History of Medicine Division, 11,000 Euclid Avenue, Cleveland 6, Ohio.

SOCIETY MEETINGS AND CONFERENCES

NOVEMBER 2, 1956–APRIL 27, 1957. Postgraduate Medical Institute. Page 785, issue of October 18.
NOVEMBER 2. Massachusetts Society of Anesthesiologists. Page 785, issue of October 18.
NOVEMBER 2–29. Consultation Clinics for Crippled Children in Massachusetts. Page 828, issue of October 25.
NOVEMBER 4–8. American Institute of Dental Medicine. Page 675, issue of October 4.
NOVEMBER 5. New England Cardiovascular Society. Page 831, issue of October 25.
NOVEMBER 6, 13, 20, 27, 29 and DECEMBER 4 and 18. Boston City Hospital House Officers' Association. Page 875.
NOVEMBER 7–9. American College of Obstetricians and Gynecologists. Page 731, issue of October 11.
NOVEMBER 12–16. American Public Health Association. Page 675, issue of October 4.
NOVEMBER 14 and 28 and DECEMBER 12. Walter E. Fernald State School. Page 728, issue of October 11.
NOVEMBER 14–22. Pan-Pacific Surgical Association. Page 490, issue of September 6.
NOVEMBER 15 and JANUARY 17, 1957. Arthritis Study Unit. Page 831, issue of October 25.
NOVEMBER 18–22. Pan American Medical Association. Page 490, issue of September 6.
NOVEMBER 28. Phi Delta Epsilon. Page 831, issue of October 25.
NOVEMBER 28. Middlesex County Sanatorium. Page 831, issue of October 25.
NOVEMBER 28–30. American College of Cardiology. Page 731, issue of October 11.
DECEMBER 14, 1956, and FEBRUARY and APRIL, 1957. Massachusetts Society for Research in Psychiatry. Page 56, issue of July 5.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, NOVEMBER 8

THURSDAY, NOVEMBER 8
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Dr. John Spellman and staff. Saint Elizabeth's Hospital.
8:00–9:00 a.m. Medical Journal Club. Joslin Auditorium, New England Deaconess Hospital.
*8:45–9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Medical Grand Rounds. Dr. Sylvester McGinn and staff. Saint Elizabeth's Hospital.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:00 m. Clinicopathological Conference. Dr. Benjamin Castleman and associates. Pathology Amphitheater, Massachusetts General Hospital.
*12:15–1:15 p.m. Orthopedic Clinic. Amphitheater, Peter Bent Brigham Hospital.
*3:00 p.m. Thoracic Conference. The Pneumonias. Dr. Paul Fremont-Smith. Main Amphitheater, Peter Bent Brigham Hospital.
5:00 p.m. Case Presentation and Pathological Discussion Followed by a Subject of Special Presentation. Joslin Auditorium, New England Deaconess Hospital.

FRIDAY, NOVEMBER 9
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Members and Guests of the Joslin Clinic. Sulfonylurea Compounds. Dr. Raffael Camerini. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:30 p.m. Medical Grand Rounds. Stearns Auditorium, New England Center Hospital.
*12:00 m. Pediatric Grand Rounds. Thorndike Amphitheater, Boston City Hospital.
*12:30–1:30 p.m. Surgical Grand Rounds. Stearns Auditorium, New England Center Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*2:00–3:00 p.m. Pathology Conference. Dr. James Graham. Saint Elizabeth's Hospital.
*4:00 p.m. Massachusetts Society of Anesthesiologists. Harvard Club, Boston.
*4:00–6:00 p.m. X-Ray Conference. Dr. Merrill S. Sosman. Stearns Auditorium, New England Deaconess Hospital.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.
*4:30 p.m. Neuroradiologic Conference. X-Ray Conference Room, New England Deaconess Hospital.

SATURDAY, NOVEMBER 10
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*8:30–10:00 a.m. Surgical Grand Rounds. Drs. Charles G. Child, III, A. J. A. Campbell and staff. First (Tufts) Surgical Service, New Cheever Amphitheater, Dowling Building, Boston City Hospital.
*9:00–10:00 a.m. Anesthesiology Conference. Dr. Benjamin Etsten. Anesthesia Laboratory, New England Center Hospital.
*9:30–11:00 a.m. Surgical House Officers' Conference. Second-Floor Conference Room, Carney Hospital, Dorchester.
*10:30 a.m. Teaching Ward Rounds. Ward South 2, Free Hospital for Women.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Hematology Conference. Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

MONDAY, NOVEMBER 12
*2:00–3:00 p.m. X-Ray Conference. Dr. William Carey. Saint Elizabeth's Hospital.

TUESDAY, NOVEMBER 13
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical Grand Rounds. Pathology Conference Room, Carney Hospital, Dorchester.
*10:30 a.m. Medical Grand Rounds. Main Conference Room (Ground Floor), Lemuel Shattuck Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m.–1:00 p.m. Pediatric Grand Rounds. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Cardiac Conference. Drs. Magendantz and L. Selverstone. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. X-Ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Hematology Conference. Dr. Mario Stefanini. Saint Elizabeth's Hospital.
*5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.
*5:00–6:00 p.m. Service Meeting Followed by Clinical Conference (Medical, Surgical, Obstetric). Faulkner Hospital.

WEDNESDAY, NOVEMBER 14
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. Deaconess II, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Auditorium, Carney Hospital, Dorchester.
*9:00–10:00 a.m. Surgical Grand Rounds. Massachusetts Memorial Hospitals.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Orthopedic Grand Rounds. Bigelow Amphitheater, White 3A, Massachusetts General Hospital.
*11:00 a.m.–12:00 m. Pediatric Conference for Practitioners. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:00 m.–1:00 p.m. Boston State Hospital Psychiatry Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*12:00 m.–1:00 p.m. Roentgen Diagnostic Conference. 5th-floor teaching unit, Beth Israel Hospital.
*12:00 m.–1:00 p.m. Neurology, Neurosurgery and Psychiatry Conference. Drs. John F. Sullivan, Justin Hope and Bertram Selverstone. Stearns Auditorium, New England Center Hospital.
*12:00 m.–1:00 p.m. Pediatric Medical-Surgical Rounds. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*12:00 m.–1:00 p.m. Pediatric Clinicopathological Conference. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:15 p.m. Vascular Rounds. Drs. Edward A. Edwards and Chilton Crane. D-Main, Peter Bent Brigham Hospital.
*12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*1:00 p.m. Massachusetts General Hospital Hand Clinic. The Clinics of the Massachusetts General Hospital.
*2:00 p.m. Rectal Clinic. Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Pediatric Conference for Practitioners. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.
*6:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*6:30 p.m. Lahey Clinic Lecture. Pituitary Disease and Tumors. Drs. Lewis M. Hurxthal and Charles A. Fager. Joslin Auditorium, New England Deaconess Hospital.

*Open to the medical profession.